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Adrenal response after trauma is affected by time after trauma and sedative/analgesic drugs

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ABSTRACT

Background: The adrenal response in critically ill patients, including trauma victims, has been debated over the last decade. The aim of this study was to assess the early adrenal response after trauma.
Methods: Prospective, observational study of 50 trauma patients admitted to a level-1-trauma centre. Serum and saliva cortisol were followed from the accident site up to five days after trauma. Corticosteroid binding globulin (CBG), dehydroepiandrosterone (DHEA) and sulphated dehydroepiandrosterone (DHEAS) were obtained twice during the first five days after trauma. The effect of time and associations between cortisol levels and; severity of trauma, infusion of sedative/analgesic drugs, cardiovascular dysfunction and other adrenocorticotropic hormone (ACTH) dependent hormones (DHEA/DHEAS) were studied.
Results: There was a significant decrease over time in serum cortisol both during the initial 24 h, and from the 2nd to the 5th morning after trauma. A significant decrease over time was also observed in calculated free cortisol, DHEA, and DHEAS. No significant association was found between an injury severity score ≥ 16 (severe injury) and a low (<200 nmol/L) serum cortisol at any time during the study period. The odds for a serum cortisol <200 nmol/L was eight times higher in patients with continuous infusion of sedative/analgesic drugs compared to patients with no continuous infusion of sedative/analgesic drugs.
Conclusion: Total serum cortisol, calculated free cortisol, DHEA and DHEAS decreased significantly over time after trauma. Continuous infusion of sedative/analgesic drugs was independently associated with serum cortisol <200 nmol/L.

Introduction

Activation of the hypothalamic–pituitary–adrenal (HPA)-axis with increased levels of cortisol is essential for survival after major trauma and critical illness in general to meet altered physiological and metabolic needs [1,2].

Insufficient cortisol levels and need for corticosteroid treatment has been proposed in hypotensive critically ill patients who respond poorly to fluids and vasoconstrictors, and a concept of critical illness-related corticosteroid insufficiency (CIRCI) has been described [2–4]. However, corticosteroid treatment induce hyperglycaemia, gluconeogenesis, protein catabolism, lipolysis, and immunosuppression – all unwanted side effects in a critically ill or severely traumatised patient [5].

Which patients benefit from corticosteroid treatment is still not conclusive [4,6,7].

Recommendations for assessment of adrenal insufficiency in critically ill patients has been based upon a random total serum cortisol taken at any time, or a defined cortisol response to corticotropin (ATCH) stimulation (delta cortisol), although the usefulness of both these diagnostic tools is now debated [3,4,8]. The most commonly used cut-off level for adrenal insufficiency in critically ill patients in general is a random serum cortisol of <10 μg/dL (276 nmol/L). In trauma patients cut-off levels from <200 nmol/L to 690 nmol/L have been suggested [2,9–13].

Duration between impact and cortisol sampling is probably of importance when assessing cortisol levels, but data on cortisol levels over time in critical illness and trauma are sparse [14].

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A potential pitfall when assessing cortisol levels is the use of sedative and analgesic drugs, which decrease sympathetic activity, and may modify cortisol release [15]. In most published studies of cortisol levels, the use of sedative drugs, except for etomidate, is rarely presented [16,17].

Furthermore, only 7–10% of total serum cortisol is free and biologically active, whereas approximately 90% is bound to corticosteroid binding globulin (CBG) and albumin [18]. In addition, capillary leakage and decreased protein synthesis in critically ill patients may result in false low total serum cortisol levels, whereas free cortisol levels may be adequate. Free cortisol can be measured using equilibrium dialysis, not easily available for clinical routine, or can be calculated from total serum cortisol and CBG-levels using Coolens' equation [19]. Only unbound cortisol passes to saliva; thus, free cortisol can be estimated by measurement of cortisol in saliva, which correlates well with free cortisol [18,20,21].

Considering the difficulties in evaluating cortisol in critically ill patients, other markers of adrenal function have been proposed, including dehydroepiandrosterone (DHEA) and its sulphated metabolite (DHEAS), normally released synchronously with cortisol in response to ACTH [22,23].

This study evaluated total serum cortisol, calculated free cortisol, and saliva cortisol in trauma patients from accident site to five days after trauma. As an additional measure of adrenal cortex function, DHEA and DHEAS were analysed.

The primary aim of this study was to evaluate changes in adrenal response over time after trauma (exposure to high kinetic energy). Secondary aims were to evaluate associations between subnormal total serum cortisol levels (defined as $<$200 nmol/L) and; severity of trauma, continuous infusion of sedative/analgesic drugs, and cardiovascular dysfunction. We hypothesised that adrenal response would be influenced by time after trauma, and that serum cortisol levels would be associated with severity of trauma, continuous infusion of sedative/analgesic drugs, and cardiovascular dysfunction.

Patients and methods

Study design

This is a prospective, observational study of adult trauma patients, admitted after a trauma alert, to Umeå University Hospital, Sweden. Patients were consecutively enrolled from February 2008 until January 2010.

A trauma alert is activated when a trauma patient is involved in a high velocity accident and/or has prehospitally affected vital parameters. Before initiation of the study we investigated the frequency of activated trauma alerts at the emergency department. It was found that approximately 60 trauma alerts were activated each year. A study period of two years was therefore considered sufficient to include the number of patients needed to answer hypothesised questions on association between adrenal insufficiency and clinical factors.

Inclusion criteria; activated trauma alert, age $\geq$ 18 years, admittance to the intensive care unit (ICU) or a surgical ward. Exclusion criteria; known hypothalamic, pituitary, adrenal, or severe liver disease, treatment with glucocorticoids within 12 months before trauma, current treatment with oestrogen/anticonceptives/antifungal drugs, pregnancy, or breastfeeding.

The actual, or as accurately as possible, time of impact was defined as T_0.

Study design is outlined in Fig. 1.

Patient management and scoring

Patients were treated according to the Prehospital Trauma Life Support (PHTLS®) and Advanced Trauma Life Support (ATLS®) concepts. Patients with traumatic brain injury (TBI) were treated with an intracranial pressure-targeted therapy [24]. Sedative/analgesic drugs used in continuous intravenous infusion were midazolam or propofol (except one patient who received thiopental one day), morphine, or fentanyl. Continuous epidural drugs used were bupivacain with or without adrenalin and/or fentanyl. No patients received etomidate at any time before or during the study period.

Two scoring scales were used for evaluation of injury severity and organ failure; the injury severity score (ISS), and the sequential organ failure assessment (SOFA) score (circulatory assessment only) [25,26]. The SOFA score evaluates organ failure from zero (no organ failure), to four (severe organ failure). Cardiovascular dysfunction was in this study defined as SOFA circulation score $\geq$3, indicating use of pharmacological cardiovascular support. ISS was evaluated once at admission, and SOFA circulation score was evaluated during each 24 h interval, and the most divergent value was noted.

Laboratory parameters

Saliva cortisol was obtained by using a specialised test-tube containing a cotton swab (Sarstedt, Salivette, Orion Diagnostica,

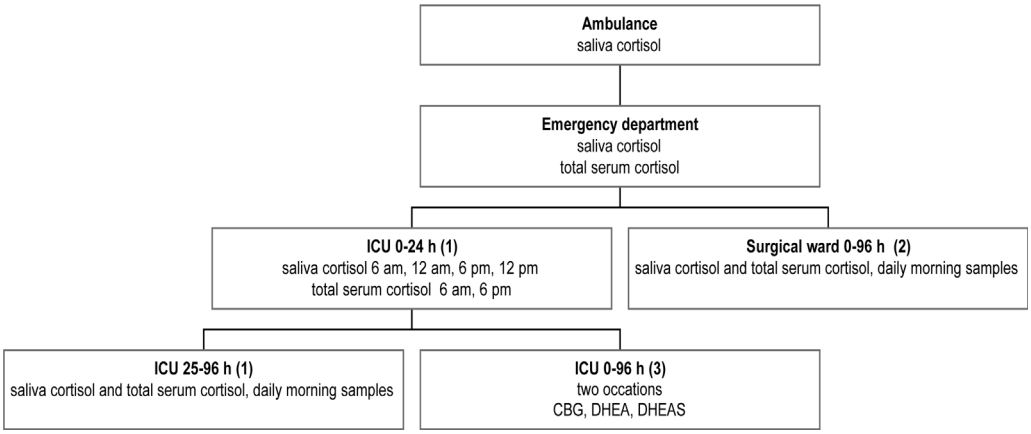

Fig. 1. Study design. The different locations (ambulance, emergency department, intensive care unit and surgical wards) where laboratory sampling was performed, type of laboratory parameter and time-points for sampling are given. h = hours; CBG = corticosteroid-binding globulin; DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate. 1 = independently of time of arrival to the ICU, serum and saliva cortisol were obtained at the fixed time points shown during the first 24 h. Thereafter, morning serum and saliva cortisol were obtained daily; 2 = independently of time of arrival to the surgical ward, morning serum and saliva cortisol were obtained daily; 3 = CBG, DHEA, and DHEAS were taken at two time-points during the study period, sample number one in the time-interval 0–24 h after trauma and sample number two in the time interval 25–96 h after trauma.