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# Monitoring of Serum Total Cortisol Level in Burned Traumatic Patients

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## Abstract

**Background:** Systematic inflammatory syndrome causes death in many conditions. Inflammation and anti-inflammation parameters variation monitoring were done by different clinical and lab methods, however, determining the progression of inflammation is very important for on time interference, gaining best results, and cost controlling. In this condition, adrenal insufficiency's variation causes water and electrolyte disorders, circulatory failure, and uncontrolled progression of inflammatory response, which is very important. Routine serum total cortisol level monitoring for SIRS is not advised as yet, and corticosteroid was used blindly according to hemodynamic condition and physician diagnosis.
**Objectives:** In this pilot study, the ability of first three days monitoring serum total cortisol level in SIRS of burned ICU traumatic patients was studied for outcoming improvement.
**Methods:** A total of 60 patients, 15 - 70 years old, < 80% burn, with systemic inflammatory response syndrome, during first three days of admission in the ICU, that weren't included in the exclusion criteria (patients with history of clinical adrenal insufficiency or corton usage, or recent drug history of etomidate or ketoconazole), were divided randomly between two groups with 30 patients. The first group considered under the routine clinical treatment and in the second group, besides the routine methods cortisol daily measurement at 8 o'clock, was done during three days to find the cortisol level under 15 ug/dL, and replacement therapy with 50 mg hydrocortisone IV, four times a day.
**Results:** None of the patients had a cortisol drop during their first three days. Among patients with cortisol more than normal, 20% (6 patients) died.
**Conclusions:** Despite the fact that total serum cortisol drop during systemic inflammatory response syndrome may happen, it is not prevalent, however, it is wise to consider it as an effective parameter on monitoring of treatment measures.

*Keywords:* SIRS, Cortisol, Adrenal Insufficiency

## 1. Background

In 1992, the American College of Chest Physicians and the American Health Care Association introduced systemic inflammatory response syndrome (SIRS) as definitions of systemic inflammatory response syndrome, sepsis, shock, and multiple organ failure. The purpose of the definition of SIRS is determination of the clinical response to the injuries due to the infectious or noninfectious agent. Systemic inflammatory response syndrome (SIRS) is characterized by the following factors: the patients were involved with body temperature more than 38°C or less than 36°C, the heart rate more than 90 bpm, respiratory rate more than 20 times per minute, pressure of carbon dioxide gas less than 32 mmHg, and the white blood cell count more than 12000 or less than 4000. The SIRS is non-specific and can be due to trauma, inflammation, ischemia, infection, or multiple injuries (1, 2).

The SIRS has the same pathophysiological features with inflammatory cascade, however, it has minor differences at the onset of cascade. Many researchers consider this syndrome as a native defense mechanism. The inflammation is the body's response to non-specific injuries caused by chemical stimuli, trauma, or infection. Inflammatory cascade is a complex process that includes humoral and cellular responses, complexes, and cytokine cascades. Bone et al., summarized the best relationship between the complex interactions and SIRS in a three-step process. At the first stage, the cytokines are produced by the immune cells in place after an injury; the local production of cytokines causes a cellular inflammatory response and induces improvement of ulcer healing by the reticuloendothelial system; this process is essential for nonspecific defense. Local inflammation in the skin and sub-

cutaneous soft tissue is characterized by classic redness, swelling, pain, warmth, and loss of function (3).

At the second stage, the low quantities of local cytokines are released into the bloodstream and improves local responses. This stimulates the growth factors and accumulates macrophages and platelets. This response is typically controlled by the reduction of pre-inflammatory mediators and the release of intrinsic antagonists; the goal is to maintain homostasis. At this stage, some symptoms including mild body temperature may appear.

In the end stage, if homeostasis is not maintained and the inflammatory stimuli exist in the systemic circulation of the body, a large systemic reaction occurs. The distribution of cytokines leads to activation of multiple humoral cascades and activation of the endothelial reticulum system subsequently cause loss of circulatory integrity, subsequently leading to organ dysfunction (2, 3).

The role of glucocorticoids in the pathophysiology of acute illnesses was interested for researchers due to the fact that adrenal glands are essential for survival under physiological stress conditions (4, 5); the clinical studies of cortisone demonstrated potential role of corticosteroids in the treatment of infections (6, 7).

The hypothalamus secretes the corticotropin releasing hormone (CRH) under the threat of hemostasis, which results in the release of adrenocorticotropin (ACTH) from the anterior pituitary and induces cortisol secretion from the adrenal glands.

The normal level of cortisol is between five to 24 $\mu$g/dL, which is strongly dependent on hourly specimen taking overnight (7). The hypothalamus-adrenal axis (HPA) activates under physiological stress (such as major surgery, pressure drop, severe infection) and its daily changes disappear (8, 9), subsequently, levels of cortisol up to 40 to 50 $\mu$g/dL (2, 8, 10-13), as well as metabolism and function of cortisol may change due to acute illness and decrease cortisol destruction (due to inhibition of expression and function of cortisol metabolizing enzymes); in addition, corticotropin levels are suppressed due to a high level of cortisol (13). Renal dysfunction may increase the half-life of cortisol in circulation. The plasma concentration of both cortisol bounding globulin (CBG) and cortisol bounding albumin reduced, subsequently free cortisol (physiologically active form of the hormone) concentration increase (2, 14, 15).

The cytokines, due to inflammatory may increase the affinity of glucocorticoid receptors to cortisol, and increase the concentration of peripheral precursors of cortisol (2, 16, 17).

The defects of HPA axis in head injuries, weaknesses of central nervous system, pituitary infarction, adrenal hemorrhage, infections, malignancies, and previous use of glucocorticoids can occur (2, 18-23).

Several studies have found that both low and high levels of serum cortisol increase mortality (24-26). In sick patients, the level of cortisol bounding globulin (CBG) reduces the protein-bounding cortisol and increases the free cortisol level, therefore, there is a shift from an inactive form (protein-bounding cortisol) to physiologically active form (free cortisol) and it suggests that the standard method of measuring plasma cortisol, which measures the total plasma cortisol concentration, estimates the activity of the axis of HPA less than actual, and the free cortisol measurement in the evaluation of the HPA axis is more accurate (27).

Systemic inflammatory response syndrome (SIRS) occurs in many conditions and leads to mortality such as sepsis. Sepsis alone causes more than a quarter of the mortalities and evaluation of changes in various inflammatory factors have been carried out by different clinical and laboratory methods. However, in spite of the availability, specificity and the effectiveness of these methods such as, the determination of the changes leading to the development of inflammation in a short time for timely intervention, achieving the best results, and controlling costs are very important. The Adrenal insufficiency is important for changes in water and electrolyte and circulatory failure due to vascular tone and also for uncontrolled progression of inflammatory responses. The measurements of cortisol have not been evaluated for SIRS.

Many physicians prescribe corticosteroids for SIRS patients; the importance and outcome of this issue has not been discussed so far.

## 2. Objectives

The aim of the study was evaluation of secretary cortisol levels from adrenal response to burn trauma. If cortisol is reduced, treatment and care will be increased, as well as interventions for acquired adrenal insufficiency.

## 3. Methods

A total of 60 patients, 15 - 70 years old, < 80% burn, with systemic inflammatory response syndrome, during the first three days of admission in the ICU, that weren't included in the exclusion criteria (patients with history of clinical adrenal insufficiency or corton usage, or recent drug history of etomidate or ketoconazole), divided randomly between two groups with 30 patients. The first group was considered under the routine clinical treatment and the second group, besides the routine methods cortisol daily measurement at 8 o'clock, was done during three

days to find the cortisol level under 15 ug/dL, and replacement therapy with 50 mg Hydrocortisone IV, four times per day.

The results of quantitative variables were expressed as mean and standard deviation (mean ± SD) and were expressed as percentage for the class qualitative variables. Comparison between quantitative variables was performed by *t*-test or if there was an abnormal distribution by Mann-Whitney test. A comparison between qualitative variables was also performed using Chi-square test or Fisher's exact test. Correlation between quantitative variables was investigated using Pearson correlation coefficient and Spearman rank correlation tests. Data were analyzed by SPSS software version 25 for statistical analysis. The significance level was less than 0.05.

## 4. Results

Table 1 shows the demographic data of the patients in the study. Of the 30 patients evaluated, six patients were female and 24 patients were male. Six patients died and 24 of them lived in the ICU ward of Shahid Motahari Hospital.

The mean and standard deviations of variables such as body temperature, leukocyte count, age, heart rate, respiratory rate, carbon dioxide, non-survivor time in the dead group, duration of survival, and burn percentage were shown in Table 2.

**Table 1.** Patients' Demographic Information

| Variables | Value[a] |
|---|---|
| **Male** | 24 (80) |
| **Female** | 6 (20) |
| **Non-survivor** | 6 (20) |
| **Live** | 24 (80) |

[a] Values are expressed as No. (%).

**Table 2.** Demographic Data of the Variables

| Variables | Max | Min | Value[a] |
|---|---|---|---|
| **Age** | 67 | 16 | 32 ± 14.1 |
| **Body temperature** | 39.2 | 36.5 | 37.3 ± 0.6 |
| **Leukocyte count** | 39 | 3 | 15.4 ± 10.5 |
| **Heart rate** | 160 | 80 | 118.5 ± 19.8 |
| **Respiratory rate** | 28 | 12 | 21 ± 4.4 |
| **Carbon dioxide** | 55 | 27 | 36.6 ± 7.8 |
| **Non-survivor time** | 43 | 4 | 15.8 ± 12 |
| **Burn percentage** | 75 | 5 | 41.8 ± 17.2 |

[a] Values are expressed as mean ± SD.

Table 3 shows standard deviation and P value in variables between two groups (non-survivor -survivor). The data were analyzed using non-parametric Mann-Whitney test. The results were demonstrated that variables including survival time, body temperature, and burn percentage were significantly different among the studied groups.

Friedman test was used to calculate the difference change in concentration of cortisol; the cortisol daily measurement at 8 o'clock was done during 3 days. According to the results, the mean concentration of cortisol in the non-survivor group was higher than the survivor group. The concentration of cortisol decreased during the study in both groups. Finally, change in concentration of cortisol was not significant in the study (P value = 0.58) (Table 4).

Systems that estimate the risk of hospital mortality based on the severity of disease lesions, particularly in the field of intensive care, have become increasingly popular over the past 20 years. The first introduced acute physiology and acronym assessment (APACHE) in 1981 and the simplified acute physiology score (SAPS) in 1988. Further

**Table 3.** The Difference in Mean of Variables in the Studied Groups

| Group | Value[a] | P Value |
|---|---|---|
| **Leukocyte count** | | 0.16 |
| Survivor | 13.8 ± 9.6 | |
| Non-survivor | 21.6 ± 12.4 | |
| **Heart rate** | | 0.054 |
| Survivor | 115 ± 17.8 | |
| Non-survivor | 132.5 ± 23 | |
| **Respiratory rate** | | 0.23 |
| Survivor | 21.6 ± 3.9 | |
| Non-survivor | 18.6 ± 6.1 | |
| **Carbon dioxide** | | 0.9 |
| Survivor | 36.6 ± 7.8 | |
| Non-survivor | 38.8 ± 8.4 | |
| **Non-survivor time** | | 0.03 |
| Survivor | 30.2 ± 3.8 | |
| Non-survivor | 16.5 ± 12.5 | |
| **Burn percentage** | | 0.05 |
| Survivor | 39 ± 14.8 | |
| Non-survivor | 52.8 ± 23.2 | |
| **Body temperature** | | 0.008 |
| Survivor | 37.5 ± 0.6 | |
| Non-survivor | 36.8 ± 0.3 | |

[a] Values are expressed as mean ± SD.

**Table 4.** The Change in Concentration of Cortisol

| Group | Value[a] |
|---|---|
| **Day 1** | |
| Survivor | 60.7 ± 21.1 |
| Non-survivor | 66.7 ± 18.3 |
| **Day 2** | |
| Survivor | 53.8 ± 17.7 |
| Non-survivor | 59 ± 17.6 |
| **Day 3** | |
| Survivor | 46.4 ± 16.8 |
| Non-survivor | 50.6 ± 19.4 |

[a] Values are expressed as mean ± SD.

**Table 5.** Changes in Apache 3 Score

| Group | Value[a] | P Value |
|---|---|---|
| **Apache score at the beginning of follow up** | | 0.001 |
| Survivor | 34.4 ± 9.8 | |
| Non-survivor | 68.8 ± 25.1 | |
| **Apache score at the end of follow up** | | 0.001 |
| Survivor | 27 ± 10 | |
| Non-survivor | 74 ± 26.8 | |

[a] Values are expressed as mean ± SD.

**Table 6.** Changes in SOFA Score

| Group | Mean of SOFA Score ± SD |
|---|---|
| **Day 1** | |
| Survivor | 3.1 ± 1.5 |
| Non-survivor | 5.6 ± 2.6 |
| **Day 2** | |
| Survivor | 3.2 ± 1.5 |
| Non-survivor | 5.6 ± 2.3 |
| **Day 3** | |
| Survivor | 3.2 ± 1.6 |
| Non-survivor | 6.4 ± 1.6 |
| **Day 4** | |
| Survivor | 3.2 ± 1.4 |
| Non-survivor | 6 ± 1.8 |
| **Day 5** | |
| Survivor | 3.2 ± 1.5 |
| Non-survivor | 5.6 ± 2.3 |
| **Day 6** | |
| Survivor | 2.6 ± 1.2 |
| Non-survivor | 5.8 ± 2.1 |
| **Day 7** | |
| Survivor | 2.2 ± 1.2 |
| Non-survivor | 5 ± 1.5 |

research led to improved versions of APACHE II (28) was developed in 1985 and SAPS II (29) in 1993. The APACHE III version (29) is now generally used and its version IV is being reviewed and developed by the HIS system of hospitals. In addition, the sequential organ failure assessment (SOFA) score is used to follow up a person's condition throughout settling in an ICU to find out the level of a person's organ function or failure. Both SOFA and APACHE scores were recorded as clinical factors (30); the results demonstrated an increase in SOFA score for the non-survivor group than that of survivors. However, this difference in SOFA score was not statistical significance in the study groups (P value = 0.6). Changes in Apache 3 score were recorded at the beginning and the end of follow up of patients (Tables 5 and 6). According to the results of the study, the difference in mean Apache score between both survivor and non-survivor groups was statistical significance.

## 5. Discussion

In the study, most patients (80%) were men who were expected to be more involved with addiction and hazardous occupations. The average age of the patients was 32 years. Due to the relative young age of the patients, the role of education at school is important to controlling and preventing.

The average respiratory rate in the survivor group (21.6) was higher than non-survivor group (18.6), although it was not statistically significant. The average respiratory rate is 20, with a high average of carbon dioxide (about 36), despite the average percentage of burns (40%), it indicates high levels of opioid usage in non-survivor group. Therefore, the opioid usage may cause reductions in average respiratory rate in the non-survivor group and can have an unfavorable effect on the outcome of the treatment.

The average heart rate was higher in the non-survivor group (130) than survivor group (115), although it is not statistically significant, it indicates that the general status of the non-survivor patients was worse. Due to the fact that the mean percentage of burns in the survivor group (39%) was lower than non-survivor group (52.8%), it was statistically significant. However, in order to be more similar to the statistical population, the burn percentage was not over 80%. Therefore, this high percentage of burns and stress caused by it, in non-survivor group, can be due to the worse general status of them.

The non-survivor group died after the second week, at this time, the main cause of deathis resistant infections; therefore, control of long-term resistant infections is very important in the field of epidemiological. Strategies such as control of personnel and equipments, limitation of contact in nonprofessional training teams with infections patients, hand hygiene, minimizing the need for intravenous nutrition, using of minimal sedation, and using of new antibiotics is very important for controlling mortality.

The mean concentration of cortisol in the non-survivor group was higher than the survivor group. The concentration of cortisol decreased during the study in both groups. Finally, change in concentration of cortisol was not significant in the study (P value = 0.58). Animal studies that have shown fluid therapy for burn patients depending on the percentage of burns causes increase excretion of cortisol; however, the expression of cortisol synthesizing genes does not increase (31). In our study, urinary cortisol was not measured, however, changes in serum cortisol levels did not reach the therapeutic range after three days.

Aissa et al. reported a case report of a 60-year-old patient with only 35% burns, in spite of controlling regeneration, the patient was rapidly treated with resistance-shock (32).

This critical drop in cortisol levels was not show in the study, and all patients survived for more than a week. The disruptive factor was that the center of reference was in fact a referral hospital, which may be that the patient suffered a severe cortisol decline in the previous stage and died with a shock, therefore, it was not included in the assessment.

Fuchs et al. evaluated 20 corticotropin-releasing hormone tests in referral burned patients after one day. They demonstrated cortisol secretion in 7 of 20 patients and showed developed adrenal insufficiency in 4 patients. This indicated the abbreviated burn severity index correlate with the risk of developing adrenal insufficiency (P = 0.008). In addition, they reported a higher mortality rate in adrenal insufficiency patients; however, this observation was not significant (P = 0.11). They recommend that further studies should be performed to benefit from cortisol replacement (33).

Endocrinological imbalance has been investigated by significant amount of studies specifically on changes in cortisol levels in burned traumatic patients (2, 34, 35). These studies indicated an increase in cortisol level comeback to severe trauma (36-38).

The mean Apache score of survivor group was lower than non-survivor group, which is statistically significant and due to a slight decrease. This score indicates failure to improve the general condition of non- survivor patients.

SOFA score were recorded as a clinical factor for organ function or failure; the results demonstrated an increase in SOFA score for the non-survivor group than that of survivors, which, although not statistically significant, it indicates a worsening of the general status of the non- survivor patients at the time of arrival to hospital.

### 5.1. Conclusions

None of the patients had a cortisol drop during the first three days. Among patients with a cortisol more than normal, 20% (six patients) died. Despite, total serum cortisol drop during systemic inflammatory response syndrome may happen, it is not prevalent, however, it is wise to consider it as an effective parameter on monitoring of treatment measures. Burned patients will involve sepsis during the course of treatment; therefore, they will involve adrenal insufficiency with higher rate despite treatment. Subsequently, the proper titers of cortisol should be investigated.

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