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Surgical Trauma-Induced Adrenal Insufficiency is Associated with Postoperative Inflammatory Responses

Moto Kashiwabara[1], Masao Miyashita[1], Tsutomu Nomura[1], Hiroshi Makino[1], Takeshi Matsutani[1], Chol Kim[2], Shinhiro Takeda[2], Kiyohiko Yamashita[1], Irshad H. Chaudry[3] and Takashi Tajiri[1]

[1]Surgery for Organ Function and Biological Regulation, Graduate School of Medicine, Nippon Medical School
[2]Department of Anesthesiology and Intensive Care, Nippon Medical School
[3]Center for Surgical Research and Department of Surgery, University of Alabama at Birmingham, USA

Abstract

The hypothalamic-pituitary-adrenal axis is an essential component for the maintenance of homeostasis following trauma. Major surgical trauma often induces overwhelming inflammatory responses leading to sepsis and organ dysfunction. This study was designed to evaluate the adrenal responses both before and after various degrees of surgical trauma and to determine the incidence of postoperative relative adrenal insufficiency resulting in the marked inflammatory response often associated with postoperative complications. Fifty-one surgical patients were divided into groups who underwent major, moderate, and minor surgeries. Before the operation and during resting conditions, a short corticotropin (ACTH) stimulation test was performed in each patient. The postoperative concentrations of serum cortisol, interleukin (IL)-6, IL-10, C-reactive protein (CRP), and plasma ACTH were measured. Fifty of 51 patients were identified as responders to ACTH. The postoperative cortisol levels were the same as those obtained by ACTH stimulation in highly and moderately stressful surgeries. The increases in postoperative IL-6 and CRP levels were greatest with major surgery, intermediate with moderate surgery, and least with minor surgery. Furthermore, plasma ACTH levels increased after major and moderate surgeries; however, there was no significant differences in postoperative serum IL-10 levels. Systemic inflammatory response syndrome (SIRS) was found in 11 of 17 patients (64.7%) who underwent major surgery and in 4 of 16 patients (25%) who underwent moderate surgery ($p=0.037$). The duration of SIRS was significantly longer in patients undergoing major surgery (62 ± 20 hrs) than in patients undergoing moderate surgery (21 ± 3 hrs, $p=0.038$). Postoperative complications were more frequent in patients undergoing major surgery (41.2%) than in patients undergoing moderate surgery (6.3%, $p=0.039$). Furthermore, there were significant differences in the length of the postoperative stay among the three groups ($p<0.01$). One nonresponder had serious postoperative inflammatory complications. These results suggest that a short ACTH stimulation test performed preoperatively is a helpful method for determining the maximal cortisol response to surgical trauma and to identify high-risk individuals and that a relative postoperative adrenal insufficiency may be closely related to the decreased cortisol secretion following major surgical trauma.
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Key words: relative adrenal insufficiency, surgical trauma, short corticotropin stimulation test, cortisol, cytokines

Correspondence to Masao Miyashita, MD, Divisions of Gastroenterology, General, Breast and Transplant, Department of Surgery, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: miyashit@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

Introduction

The activation of the hypothalamic-pituitary-adrenal (HPA) axis is an essential component for the maintenance of homeostasis following injury[1,2]. Cortisol has various vital supportive roles, and its secretion is regulated via the HPA axis[3,4]. Cortisol is required for immune function, synthesis of catecholamines, adrenergic receptor synthesis and action, maintenance of vascular tone, and numerous other functions. The HPA axis is a major determinant of the patient's responses to surgical trauma, and cortisol plays a central role in modulating humoral mediators during those conditions[5–8]. Because cortisol suppresses the secretion of inflammatory cytokines, an important function of the HPA axis is to prevent severe inflammation[9]. Some studies have shown that the magnitude of the postoperative increase in serum cortisol level is positively correlated with the extent of surgery[7,8], whereas another study showed that it was not[10].

Systemic cytokine responses induced by surgical trauma may play an important role in eliciting systemic inflammatory responses to elective surgery[11,12]. Postoperative complications, so-called stress-induced organ dysfunction states, are thought to be caused by an uncontrolled inflammatory response due to the overproduction of proinflammatory cytokines[13,14], and elevated serum levels of the proinflammatory cytokine interleukin (IL)-6 have been reported to correlate with postoperative morbidity and mortality[15,16]. Elevated serum levels of the anti-inflammatory cytokine IL-10 have been reported both during and after surgery[17], and IL-10 is believed to be induced by glucocorticoids[9,10,14,18–20].

Recent studies suggest that severe sepsis and severe trauma may be associated with relative adrenal insufficiency, which may contribute to a fatal outcome[2,3,5,6,21–25]. Additionally, it has been reported that a short corticotropin (ACTH) stimulation test has good prognostic value and could be helpful in identifying patients with septic shock at high risk for death[2]. The purpose of this study was to prospectively evaluate the individual adrenal responses both before and after different degrees of surgical trauma and to determine the incidence of postoperative relative adrenal insufficiency resulting in the marked inflammatory responses often associated with postoperative complications. To evaluate the adrenal response in each subject in the resting condition, a short ACTH stimulation test was performed preoperatively. We measured serum cortisol level to examine the adrenal response, serum IL-6 and C-reactive protein (CRP) levels to examine inflammatory responses, and the serum IL-10 level to examine the anti-inflammatory response in patients who underwent surgical trauma of different degrees.

Materials and Methods

Patients

Fifty-one patients who underwent surgery of the digestive system at Nippon Medical School Hospital from January 2003 through March 2004 were enrolled in this study. Patients who had a history of treatment with corticosteroids and other hormones, preoperative inflammatory reaction within 7 days of surgery, preoperative complications such as liver cirrhosis or diabetes mellitus, or old tuberculosis lesions were excluded from the study. the patients were divided into three groups: a group who underwent major surgery (n=17), e.g., esophagectomy by the thoracoabdominal approach; a group who underwent moderate surgery (n=17), e.g., open abdominal surgery, including gastrectomy, colectomy, and transhiatal esophagectomy; and a group who underwent minor surgery (n=17), e.g., laparoscopic cholecystectomy. All surgeries started at 9 : 00 A.M. to minimize the confounding effect of diurnal variations in plasma ACTH and serum cortisol levels. All patients received 0.5 mg of atropine sulfate intramuscularly 60 minutes before the induction of anesthesia at 8 : 30 a.m. Epidural analgesia at an appropriate level was induced by the continuous administration of 0.2% ropivacaine and confirmed by pinprick sensation loss before the induction of general anesthesia. General endotracheal anesthesia was then induced using 1% to 1.5%

sevoflurane, 50% to 67% nitrous oxide, and 33% to 50% oxygen. Concomitant epidural anesthesia was also maintained by continuous administration of 0.2% ropivacaine at a rate of 3 to 6 mL/hour. Intraoperative muscle relaxation was facilitated by vecuronium administration. This study protocol was approved by the Ethics Committee of Nippon Medical School, and written informed consent was obtained from each subject.

Preoperative Short ACTH Stimulation Test

At the resting condition, 2 to 3 days before to the operation, a short ACTH stimulation test was performed using 250 μg of tetracosactide acetate (Cortrosyn; Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) intravenously injected at 9 : 00 A.M. to evaluate the adrenal response in each subject. Blood samples were obtained immediately before and 60 minutes after the test. Serum cortisol concentrations were measured with a two-site immunoradiometric assay (IRMA) (Immunotech, Marseille, France). The cortisol response was defined as the difference between the serum cortisol concentration 60 minutes after the test and that before the test. Subjects who were ACTH responders were identified by a response of 9 μg/dL or more[2].

Adrenal Response and Inflammatory Mediators in Surgical Trauma

Blood samples were obtained preoperatively (before anesthesia) and immediately at the end of surgery. They were immediately separated by centrifugation (3,000 rpm for 15 minutes) and stored at −70℃ until assayed.

Serum cortisol concentrations were measured with the method described for the ACTH test. Plasma ACTH concentration was measured with IRMA (Mitsubishi Kagaku Iatron, Inc., Tokyo, Japan). The concentration of serum IL-6 was measured with a chemiluminescent enzyme immunoassay (CLEIA) (Fujirebio Inc., Tokyo, Japan), and serum levels of IL-10 were measured with an enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, USA). Serum CRP concentrations were measured during the first 7 postoperative days (PODs), and the factors for postoperative systemic inflammatory response syndrome (SIRS) were monitored. Serum CRP concentrations were measured at the hospital's central laboratory. SIRS was diagnosed when at least two of the following factors were present: body temperature (>38℃ or <36℃), heart rate (>90 beats/min), tachypnea (>20 breaths/min), hyperventilation ($PaCO_2$ <32 mmHg), and white blood cell count abnormalities (>12,000 cells/mm^3 or <4,000 cells/mm^3 or 10% immature (band) forms). The postoperative complications were defined as follows: infectious complications were defined as positive culture of blood, sputum, or other bodily fluids in the presence of clinical evidence of infection; anastomotic leakage was diagnosed with esophagography or esophagoscopy.

Statistical Analysis

All analyses were performed with statistical software (Statview 5.0; Abacus Concepts, Berkeley, CA, USA). All values are expressed as means ± standard errors of the mean (SEM). Categorical variables were compared using the Chi-square or the Kruskal-Wallis test. The values of serum cortisol, IL-6, IL-10 and plasma ACTH were compared among the three groups using the Kruskal-Wallis test followed by Scheffe's post-hoc multiple comparison test. Serum CRP levels were also subjected to the same analysis. Correlations were determined by Spearman's correlation coefficient by rank. A probability (p) value of less than 0.05 was considered to indicate statistical significant.

Results

Response to Preoperative Short ACTH Stimulation Test

Fifty of 51 patients were identified as responders to ACTH, i.e., adrenal function was normal. Serum cortisol levels 60 minutes after the ACTH test increased by more than twofold over the baseline levels and no significant differences in the increased cortisol levels among the three groups were noted (30.2 ± 1.4, 29.4 ± 1.2, and 31.7 ± 1.5 μg/dL in groups which underwent major surgery, moderate surgery, and minor surgery, respectively) (**Fig. 1A**). Of the 51

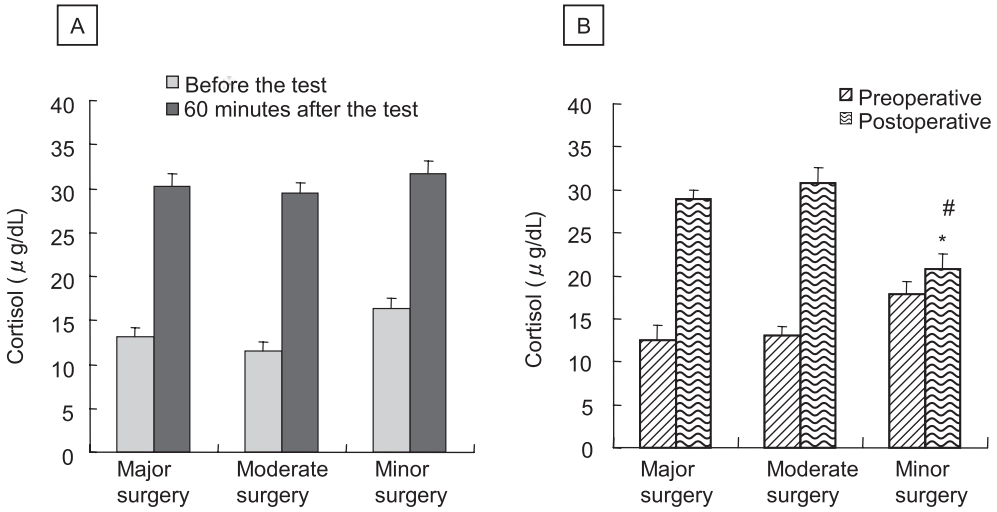

Fig. 1 Comparison of serum cortisol responses to ACTH (A) and to surgical trauma (B) among the three groups. The values are expressed as means ± SEM. *p<0.05 for postoperative serum cortisol level of patients who underwent minor surgery vs. patients who underwent major surgery. #p<0.05 for postoperative serum cortisol level of patients who underwent minor surgery vs. patients who underwent major surgery.

Table 1 Clinical features of patients excluding nonresponder

	Major surgery group (n=17)	Moderate surgery group (n=16)	Minor surgery group (n=17)	p value
Age (years)	63 ± 2	65 ± 3	62 ± 3	0.97*
Gender				0.46#
Male	13	9	10	
Female	4	7	7	
Duration of operation (min)	459 ± 32	258 ± 18	131 ± 10	< 0.01*
Blood loss (mL)	896 ± 99	480 ± 81	26 ± 18	< 0.01*

Data are presented as mean ± SEM. *Kruskal-Wallis test, #Chi-square test.

patients, only 1, who underwent moderate surgery, did not show any increase in serum cortisol level after the ACTH stimulation. This patient was the only nonresponder and is described in detail elsewhere.

Clinical Features of Responders

The clinical features of responders to ACTH are summarized in **Table 1**. There were statistically significant differences among the three groups in the duration of operation and the volume of blood loss (p<0.01). However, no significant differences in age or gender were found.

Serum Cortisol and Plasma ACTH Levels Associated with Surgical Trauma in Responders

The postoperative serum cortisol levels (28.9 ± 1.1, 30.8 ± 1.8, and 20.8 ± 1.7 μg/dL in patients who underwent major surgery, moderate surgery, or minor surgery, respectively) were significantly higher than the preoperative levels (12.5 ± 1.7, 13.0 ± 1.0, and 17.9 ± 1.5 μg/dL, respectively) in patients who underwent major surgery or moderate surgery but not in patients who underwent minor surgery **(Fig. 1B)**. In patients who underwent major or moderate surgery, the postoperative serum cortisol levels significantly correlated with the serum cortisol level after the ACTH stimulation test, whereas no correlation was found in patients who underwent minor surgery **(Fig. 2)**. The plasma ACTH levels

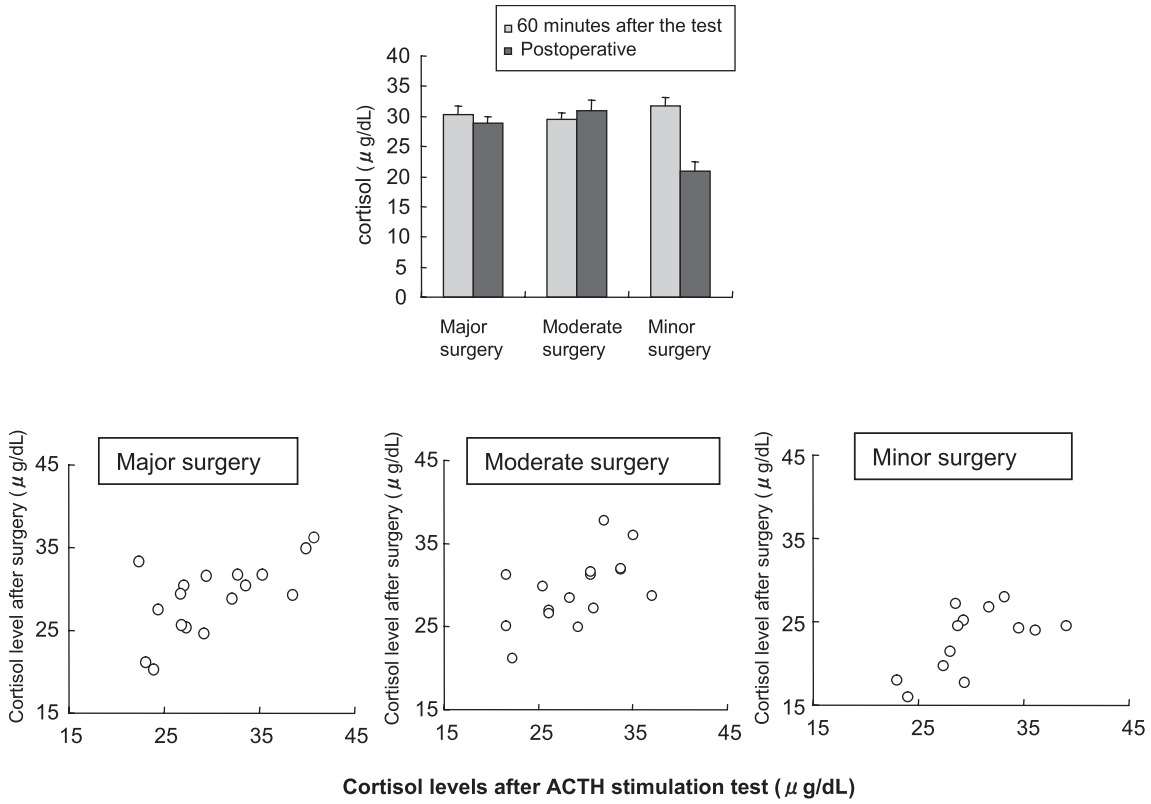

Fig. 2 Correlation between serum cortisol levels after the ACTH stimulation test and those after surgery among the three groups. The increased serum cortisol levels after the ACTH stimulation test significantly correlated with the postoperative serum cortisol level in patients who underwent major surgery or moderate surgery, whereas no correlation was found in patients who underwent minor surgery (p=0.025, r=0.64; p=0.009, r=0.57; p=0.12, r=0.35; respectively).

increased postoperatively. Although there were intersubject variations, plasma ACTH levels tended to be high in patients who underwent major surgery or moderate surgery **(Fig. 3)**.

Serum IL-6 and IL-10 Levels Associated with Surgical Trauma in Responders

The postoperative serum IL-6 levels were markedly high in patients who underwent major surgery and were significantly higher in patients who underwent moderate surgery than in patients who underwent minor surgery (463.1 ± 66.8, 192.0 ± 35.1, and 21.4 ± 3.5 pg/mL in patients who underwent major surgery, moderate surgery, or minor surgery, respectively). However, no significant differences in postoperative serum IL-10 levels were found (21.9 ± 11.8, 11.2 ± 2.6, and 21.6 ± 8.3 pg/mL in patients who underwent major surgery, moderate surgery, or minor surgery, respectively) **(Fig. 3)**.

Postoperative Serum CRP Level and Clinical Outcome in Responders

The serum CRP levels in each group peaked on POD 3 and then gradually decreased. The serum CRP levels on POD 3 in patients who underwent major surgery (18.5 ± 1.5 mg/dL) or moderate surgery (14.7 ± 1.4 mg/dL) were significantly higher than those in patients who underwent minor surgery (4.5 ± 1.4 mg/dL; $p<0.01$; **Fig. 4**). SIRS was not found in patients who underwent minor surgery but was found in 11 of 17 patients (64.7%) who underwent major surgery and 4 of 16 patients (25%) who underwent moderate surgery. There was a significant difference in the incidence of SIRS between patients who underwent major surgery and patients who underwent moderate surgery (p=0.037). Furthermore, the duration of SIRS was significantly longer in patients who underwent major surgery (62 ± 20 hours) than in patients who underwent

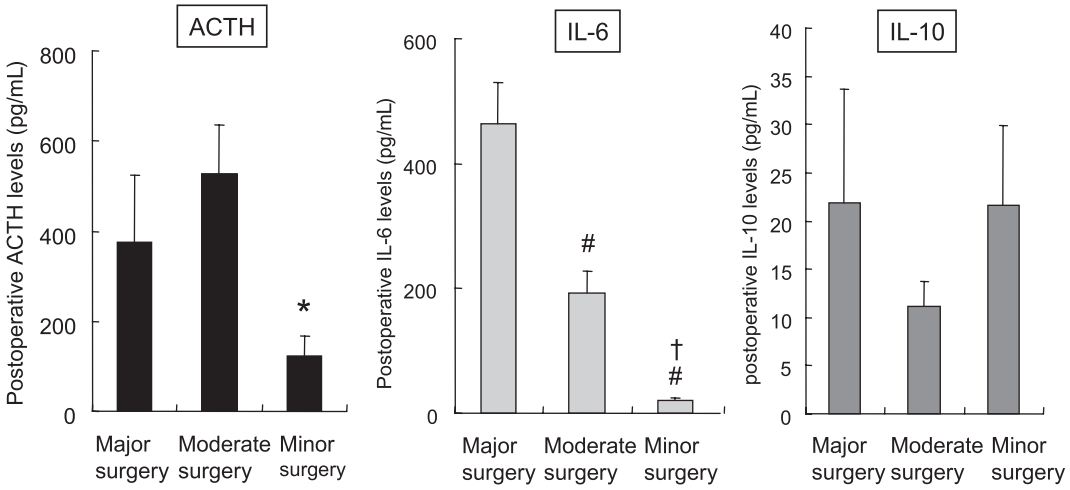

Fig. 3 Comparison of postoperative plasma ACTH levels and serum IL-6 and IL-10 levels among the three groups. The values are expressed as means ± SEM. *p<0.05 for patients who underwent minor surgery vs. patients who underwent moderate surgery. #p<0.05 for patients who underwent moderate surgery or minor surgery vs. patients who underwent major surgery. †p<0.05 for patients who underwent minor surgery vs. patients who underwent moderate surgery.

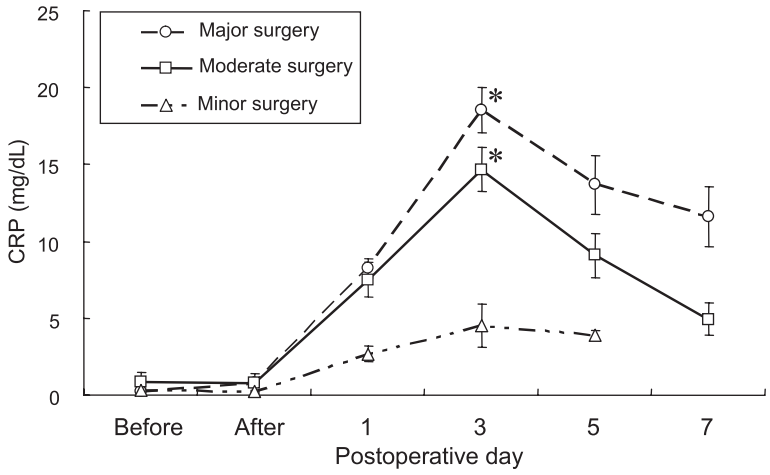

Fig. 4 Postoperative changes in serum CRP levels in the three groups. *p<0.05 for patients who underwent major surgery or moderate surgery vs. patients who underwent minor surgery on POD 3.

moderate surgery (21 ± 3 hours, p=0.038). Postoperative complications were found in 7 of 17 patients (41.2%) who underwent major surgery and 1 of 16 patients (6.3%) who underwent moderate surgery. There was significant difference in the incidence of postoperative complications between patients who underwent major and patients who underwent moderate surgery (p=0.039). Consequently, there were statistically significant differences in the postoperative stay among the three groups (p<0.01; **Table 2**).

In patients who underwent major surgery, significant differences in postoperative serum IL-6 levels and CRP levels on POD 3 were found between those with and without postoperative complications, whereas no significant differences in cortisol, IL-10, or plasma ACTH levels were found (data not shown).

Table 2 Clinical outcomes of responders

	Major surgery (n=17)	Moderate surgery (n=16)	Minor surgery(n=17)
Postoperative complications			
Present/Absent	7/10 (41.2%)*	1/15 (6.3%)*	0/17 (0%)
Surgical Site Infection	2	0	0
Pneumonia	3	1	0
Anastomotic leakage	2	0	0
Postoperative SIRS			
Present/Absent	11/6 (64.7%)*	4/12 (25%)*	0/17 (0%)
Duration of SIRS (hr)	62±20 †	21±3 †	0
Postoperative hospital stay (days)#	39.6±5.8	20.8±2.1	6.7±0.3

Data are presented as mean±SEM. SIRS=systemic inflammatory response syndrome
*$p<0.05$ for major surgery versus moderate surgery, using Fisher's exact test
†$p<0.05$ for major surgery versus moderate surgery, using Mann-Whitney U test
#$p<0.01$ using Kruskal-Wallis test

Table 3 Clinical features of a nonresponder

Age (years)	72	
Gender	Female	
Surgical procedure	Trans-hiatal esophagectomy	
Duration of operation (min)	355	
Blood loss (mL)	750	
Cortisol (μg/dL)		
Before and after the ACTH test	17.3	16.8
Before and after surgery	10	19.9
Postoperative ACTH (pg/mL)	2,000	
Postoperative IL-6 (pg/mL)	1,520	
Postoperative IL-10 (pg/mL)	6.4	
SIRS		
Present/Absent	Present	
Duration of SIRS (hr)	384	

SIRS=systemic inflammatory response syndrome

Clinical Features of Nonresponders

Only 1 patient was identified as a nonresponder to the preoperative short ACTH stimulation test. Clinical features of this patient are summarized in **Table 3**. Serum cortisol levels of this patient were 17.3 μg/dL before and 16.8 μg/dL 60 minutes after the ACTH stimulation test. This patient underwent moderate surgery and displayed preoperative and postoperative serum cortisol levels less than 20 μg/dL (10 μg/dL and 19.9 μg/dL, respectively). Postoperative plasma ACTH and serum IL-6 levels were markedly high (2,000 pg/mL and 1,520 pg/mL, respectively). The CRP levels reached a peak value on POD 3 and tended to be higher than those in patients who underwent major surgery at every time point after surgery. Postoperative SIRS developed in this patient and persisted an extremely long time (384 hours). Postoperative pneumonia and anastomotic leakage also developed in this patient.

Discussion

Several studies have suggested that a short ACTH stimulation test is helpful for identifying patients with severe illnesses who are at high risk[2,3,5,6,22–24]. Another study has found that adrenal insufficiency, as assessed with the ACTH test, is common after successful resuscitation from cardiac arrest but is not associated with severity[26]. However, this study had several limitations, such as the small

sample size and an extremely high mortality rate. In contrast, we investigated individual adrenal responses under normal conditions by means of a preoperative short ACTH stimulation test to determine whether a patient's adrenal response reflects both the postoperative adrenal response and clinical outcome. Our results show that a short ACTH stimulation test performed preoperatively seems to demonstrate an individual's maximal cortisol secretion from the adrenal glands; therefore, the test is of great significance for evaluating an individual's adrenal response and may allow high-risk individuals to be identified before a planned operation, although we only identified 1 nonresponder in this study.

We also investigated the effect of surgical stress on the levels of serum cortisol and plasma ACTH and the inflammatory responses in patients who underwent operations with various degrees of trauma. As an anti-inflammatory axis, surgical stress or surgery-induced proinflammatory cytokines (e.g., IL-6) stimulated the central nervous system to release hypothalamic corticotropin-releasing factor (CRF) and, subsequently, ACTH from the anterior pituitary gland, which then induced the secretion of cortisol from the adrenal glands[9]. Cortisol inhibits the secretion of CRF and ACTH by a negative feedback mechanism. During surgical trauma, patients with a normal HPA axis function consistently exhibit elevated total serum cortisol levels[21]. However, there is an interindividual variation in the cortisol response to stress. Studies have also reported that there is a positive correlation between the postoperative increase in serum cortisol level and the degree of surgical stress[7,8]. However, no correlation has been found between the adrenal response and the degree of surgical stress[10]. In view of these findings, we postulated that major surgery would lead to a high postoperative serum cortisol level. However, our present results indicate that the level of cortisol secreted in the blood reached a maximum, even in patients who underwent moderate surgery, e.g., open abdominal surgery, although cortisol levels varied greatly among these patients. Therefore, a severe surgical stress, such as highly stressful thoracoabdominal operation, caused relative adrenal insufficiency, which resulted in the hypersecretion of IL-6 and CRP and prominent clinical signs of SIRS. Furthermore, these variables were directly linked to the serious postoperative complications and prolonged hospitalization. For those patients who respond poorly to the ACTH test, i.e., nonresponders, surgical procedures may be harmful, and severe adrenal insufficiency is more likely occur postoperatively. It is also noteworthy that adrenal insufficiency occurs in experimental models of trauma hemorrhage[26,27] and of sepsis[28,29].

Plasma ACTH levels tended to be high in patients who underwent major or moderate surgery. We therefore speculated the following phenomena: 1) there may be an enormous prolonged stress causing a high plasma ACTH level, and 2) an insufficient level of cortisol or a limitation in cortisol secretion may fail to trigger the negative feedback mechanism of ACTH secretion. Recent studies suggest that age is associated with changes in basal or stimulated serum cortisol levels in critically ill patients[30,31]. In this study, no significant differences in age were noted between the three groups, indicating that our our results were not affected by age. The serum level of the anti-inflammatory cytokine IL-10 was also measured. Although IL-10 is believed to be induced by glucocorticoids[9,10,14,18–20], the serum IL-10 level did not correlate with either the degree of surgical stress or the cortisol level. Thus, the increase in IL-10 may be due to a more complex network of mechanisms and requires further study.

Several studies have shown that corticosteroid replacement therapy is beneficial in patients with septic shock and relative adrenal insufficiency[32–34]. Studies have also shown that the preoperative administration of corticosteroids is effective in suppressing surgery-induced excessive inflammatory responses and in preventing postoperative complications in severely stressful surgery (major surgery), such as transthoracic esophagectomy, cardiac surgery, and hepatic resection[14,18,19,35–38]. For patients who undergo extremely stressful surgery or who are identified as nonresponders to ACTH, the present study supports the notion that supportive therapy with corticosteroids is important for maintaining homeostasis and in preventing

prominent postoperative inflammatory complications.

In conclusion, a short ACTH stimulation test performed preoperatively is a useful method for determining a patient's maximal cortisol response to surgical trauma. Furthermore, stressful surgery induces relative adrenal insufficiency, leading to marked inflammatory responses. This study indicates the rationale of corticosteroid supportive therapy, which may be useful in such stressful surgeries.

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