Association between Adrenal Insufficiency and Ventilator Weaning

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Rationale: Adrenal insufficiency is a common disorder in critically ill patients with mechanical ventilation and is usually associated with higher mortality and poor clinical outcome.

Objectives: To determine whether stress dose corticosteroid supplementation can improve ventilator weaning and clinical outcome in patients with adrenal insufficiency.

Methods: A prospective, randomized, placebo controlled, double-blinded study was conducted in the intensive care unit of a tertiary teaching hospital. A total of 93 mechanically ventilated patients were enrolled in the ventilator weaning trial. Adrenal function was assessed in all patients. Patients with adrenal insufficiency were randomized to the treatment group (50 mg intravenous hydrocortisone every 6 h) and the placebo group. No significant adverse effects were observed in the treatment group (91.4%) than in the placebo group (68.6%). The weaning period was shorter in the hydrocortisone treatment group than in the placebo group. No significant adverse effects were observed in the corticosteroid treatment group.

Conclusions: For patients with respiratory failure, early identification of adrenal insufficiency and appropriate supplementation with stress dose hydrocortisone increase the success of ventilator weaning and shorten the weaning period.

Keywords: adrenal insufficiency; hypothalamic-pituitary-adrenal axis; stress dose hydrocortisone; ventilator weaning

METHODS

Patients
Chang Gung Memorial Hospital is a 3,000-bed tertiary teaching facility. The ICU is a 26-bed unit that cares for patients with critical medical conditions. The study started on May 1, 2003, and ended on December 31, 2003. All patients enrolled in the study were under mechanical ventilation for more than 72 h via endotracheal tubes. The primary etiology of their respiratory failure was recovering, and vasopressor agents and sedative medication had been discontinued for at least 24 h before the study commenced. These patients were hemodynamically stable, neurologically intact (Glasgow coma score > 11), and waiting for VW. Patients received regular corticosteroid medication before or during the admission, and patients without adequate cough reflex were excluded. The study was performed with the approval of the hospital ethics committee. Informed consent from each enrolled patient or a close relative was obtained.

Study Protocol
The study was a prospective, randomized, placebo-controlled, double-blinded study. Cortisol concentrations were measured with a competitive immunoassay using direct chemiluminescent technology (ADVIA Centaur Assay; Bayer, Leverkusen, Germany) in the clinical pathology laboratory of the hospital. The morning cortisol level (between 7:00 and 9:00 A.M.) was checked when patient condition met the VW criteria. Plasma cortisol concentrations above 25 μg/dl (694 nmol/L) were considered to reflect intact adrenal function. If the morning cortisol level was below 25 μg/dl, a high-dose adrenocorticotropic (ACTH) stimulation test was performed with a 250-μg intramuscular cosyntropin injection with blood samples taken immediately before and 60 min after the test. An intact adrenal reserve was defined as an increase in serum cortisol of greater than 9 μg/dl (250 nmol/L), whereas an increase in serum cortisol of less than 9 μg/dl was defined as AI (5, 23). Patients with AI were randomized to the treatment group (50 mg intravenous hydrocortisone every 6 h during the weaning period) and the placebo group (normal saline). In the corticosteroid supplement group, the treatment of intravenous corticosteroid covered the entire weaning period and it was shifted to oral cortisol acetate after successful weaning or weaning failure. When the weaning period ended, these patients with AI, including the placebo group and the corticosteroid group, were shifted to 75 mg oral cortisol acetate in the morning and 37.5 mg in the afternoon. Randomization was according to a computer-generated random-number table. The flow chart of the study is...
presented in Figure 1. The Acute Physiology, Age, and Chronic Health Evaluation III (APACHE III) score (24), rapid shallow breathing index (RSI) (25), etiology of respiratory failure, underlying disease, and arterial blood gas analysis were recorded for all patients before VW was attempted.

All enrolled patients underwent a protocol-driven VW strategy. The respiratory therapists screened for the weaning criteria daily.

The criteria for starting weaning were as follows:
1. No suspected increased intracranial pressure
2. No unstable coronary artery disease
3. Heart rate less than 140 beats/min
4. SpO2, greater than 92%
5. Positive end-expiratory pressure less than 8 cm H2O
6. FIO2 less than 0.35
7. Intact cough reflex

If the patient went through the spontaneous breathing trial successfully, extubation was performed. Successful weaning was defined as the patient not requiring reintubation or additional respiratory support, such as noninvasive positive-pressure ventilation within 48 h of extubation. If the patient was not weaned successfully and the total ventilator period was more than 14 d, the patient was defined as weaning failure. Tracheostomy was recommended for long-term care. All complications during VW were recorded.

Statistical Analysis
All demographic data, ICU length of stay, hospital stay, and duration of weaning were expressed as mean ± SD or frequency (%) where appropriate and were analyzed with one-way analysis of variance tests. The Bonferroni test was used for multiple comparisons among means of the three groups. The χ2 test (with Yates' correction) was applied to successful VW results and hospital mortality. Multivariate logistic regression was used to analyze the demographic variables and underlying disease between the corticosteroid group and the placebo group. A p value of 0.05 or less was considered to be statistically significant.

RESULTS
Patient Characteristics
During the study period, 472 ventilated patients were admitted to the ICU and 179 patients were evaluated for this study. Ninety-three patients who met the inclusion criteria were enrolled in the study (Figure 1). After initial evaluation of adrenal function, 23 patients were found to have normal adrenal function and 70 were diagnosed with AI. Patients with AI were randomly selected by computer to the treatment group (n = 35) and the placebo group (n = 35). Demographic data for the groups are shown in Table 1. No statistical differences among the three groups were found in terms of age, sex, APACHE III, RSI, ventilator days before randomization, or PaO2/FIO2. The mean morning cortisol level was significantly higher in the group with adequate adrenal reserve than in the AI groups. In the AI groups, there was no statistical difference between the corticosteroid treatment group and the placebo group in comparisons of morning cortisol levels. The main respiratory failure etiologies and the underlying diseases are shown in Table 2.

Successful Weaning
In adequate adrenal reserve group, 20 patients were successfully weaned from ventilator but three patients failed after extubation. In corticosteroid treatment group, 32 patients were successfully weaned, one failed the T-piece trial, and two failed after extubation. In the placebo group, 24 patients were successfully weaned, two failed the T-piece trial, and nine failed after extubation (Table 3). For patients with adequate adrenal reserve and the patients with AI receiving corticosteroid treatment, the success rate for weaning was similar. For patients with AI receiving placebo treatment, the successful weaning rate was significantly less than 72 h. At this point, if the FIO2 of the ventilator setting was over 50%, the patient was defined as unstable and excluded.
practice.

of adrenal function before weaning is useful in routine ICU extubation, thereby demonstrating an association between AI ACTH stimulation tests to determine adrenal reserve before group. This is the first study to use morning cortisol level and rate for VW and a shorter weaning duration than in the placebo extubation of patients with AI led to a significantly higher success in this study, stress dose corticosteroid supplementation before extubation of patients with AI led to a significantly higher success rate for VW and a shorter weaning duration than in the placebo group. This is the first study to use morning cortisol level and ACTH stimulation tests to determine adrenal reserve before extubation, thereby demonstrating an association between AI and extubation outcomes. The results suggest that evaluation of adrenal function before weaning is useful in routine ICU practice.

Although cortisol is one of the most widely studied hormones, it is probably one of the least understood. The definition of AI remains controversial (3, 5, 23, 26). A cortisol level greater than 25 \( \mu g/dl \) was considered adequate adrenal reserve in many textbooks and recent studies (8, 10). ACTH stimulation is essential to exclude AI, especially when the cortisol level is below 25 \( \mu g/dl \). The cut-off value of increment of cortisol after ACTH stimulation test remains debatable but an increment of less than 9 \( \mu g/dl \) (250 nmol/L) was considered insufficient in critically ill patients (5, 23). The morning cortisol level and ACTH stimulation test provide a reliable evaluation of adrenal function. In addition to playing a role in septic shock, physiologic corticosteroid replacement may be beneficial in patients with other critical illnesses, including trauma, burns, and medical and surgical conditions where AI is evident (27, 28). To date, there are no published data indicating that stress dose corticosteroids improve the success of VW in the ICU. Our study suggests that patients with adequate adrenal function have a similar success rate of VW to patients with AI receiving stress dose hydrocortisone. It can be claimed that ICUs should routinely test adrenal function before VW. In the present study, hospital mortality, ICU length of stay, and hospital stay did not statistically differ between the hydrocortisone treatment group and the placebo group, although the mean ICU length of stay was shorter in the hydrocortisone treatment

### TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF RESPIRATORY FAILURE PATIENTS BEFORE WEANING

<table>
<thead>
<tr>
<th></th>
<th>Adequate Adrenal Reserve (n = 23)</th>
<th>Corticosteroid Group (n = 35)</th>
<th>Placebo Group (n = 35)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.0 ± 14.5</td>
<td>72.0 ± 13.2</td>
<td>71.8 ± 16.3</td>
<td>0.542</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>12 (52.2)</td>
<td>17 (48.6)</td>
<td>23 (65.7)</td>
<td>0.331</td>
</tr>
<tr>
<td>APACHE III score</td>
<td>53.5 ± 22.9</td>
<td>54.0 ± 19.9</td>
<td>32.8 ± 16.8</td>
<td>0.969</td>
</tr>
<tr>
<td>RSI</td>
<td>132.8 ± 76.6</td>
<td>114.5 ± 51.9</td>
<td>134.6 ± 74.1</td>
<td>0.407</td>
</tr>
<tr>
<td>PaO2/FIO2</td>
<td>257.7 ± 90.8</td>
<td>277.9 ± 80.3</td>
<td>238.6 ± 78.6</td>
<td>0.142</td>
</tr>
<tr>
<td>Morning cortisol level, µg/dl</td>
<td>38.3 ± 20.8</td>
<td>13.7 ± 6.0</td>
<td>17.0 ± 6.0</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Ventilator days before randomization</td>
<td>5.5 ± 4.8</td>
<td>5.9 ± 5.1</td>
<td>4.9 ± 6.2</td>
<td>0.667</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** APACHE III = Acute Physiology, Age, and Chronic Health Evaluation III; RSI = rapid shallow breathing index (respiratory rate/VT).

* Under multiple comparisons, morning cortisol level of the adequate adrenal reserve group was significantly different from the adrenal insufficiency group.

### TABLE 2. ETIOLOGY OF RESPIRATORY FAILURE AND UNDERLYING DISEASES OF ALL PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Adequate Adrenal Reserve (n = 23)</th>
<th>Corticosteroid Group (n = 35)</th>
<th>Placebo Group (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>17 (73.9%)</td>
<td>27 (77.1%)</td>
<td>20 (57.1%)</td>
</tr>
<tr>
<td>Cardiogenic pulmonary edema</td>
<td>3 (13.0%)</td>
<td>2 (5.7%)</td>
<td>6 (17.1%)</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>1 (4.3%)</td>
<td>0 (0%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>1 (4.3%)</td>
<td>1 (2.9%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Sepsis*</td>
<td>18 (78.2%)</td>
<td>30 (85.7%)</td>
<td>26 (74.3%)</td>
</tr>
<tr>
<td>Shock</td>
<td>1 (4.3%)</td>
<td>5 (14.3%)</td>
<td>7 (20.0%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (8.6%)</td>
<td>3 (8.6%)</td>
<td>5 (14.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (4.3%)</td>
<td>1 (2.9%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>ESRD</td>
<td>6 (26.1%)</td>
<td>7 (20.0%)</td>
<td>10 (28.6%)</td>
</tr>
<tr>
<td>CVD</td>
<td>6 (26.1%)</td>
<td>4 (11.4%)</td>
<td>8 (22.9%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4 (17.3%)</td>
<td>4 (11.4%)</td>
<td>3 (8.6%)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>4 (13.0%)</td>
<td>9 (25.7%)</td>
<td>7 (20.0%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3 (13.0%)</td>
<td>3 (8.6%)</td>
<td>2 (5.7%)</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** CVD = cerebral vascular disease; ESRD = end-stage renal disease.

* Sepsis was defined as systemic inflammatory response syndrome with a proven or suspected microbial etiology.
group compared with the placebo group. Because such results could reflect the influence of multiple factors on hospital mortality, ICU length of stay, and hospital stay, corrected AI may not produce improvement. The limitation of our study is the small patient number in each group. However, the result inspired us to conduct a larger and multicenter study to prove the present finding. Another limitation of the study is that we cannot explain the result from physiology. A good animal model study is required to clarify the underlying mechanism.

Although corticosteroid supplementation has benefited patients with septic shock in recent studies (4), the actual pathophysiology remains unclear. Keh and coworkers (29) reported that low-dose hydrocortisone supplementation increased arterial pressure and systemic vascular resistance, and decreased inotropic agent requirements in patients with septic shock. The increased respiratory work in a VW trial challenges the cardiopulmonary system and HPA axis, potentially leading to hemodynamic instability. Hypoglycemia caused by AI may also contribute to hemodynamic instability. Possibly, low-dose hydrocortisone therapy improves VW success rates by improving hemodynamic stability.

A high incidence of AI (>75%) in patients with severe sepsis was reported by Annane and coworkers (4). The high prevalence (75.3%) of AI in our study was surprising and implied a problem of ignorance. Presentation of AI is nonspecific and asymptomatic. Cooper and Stewart (23) suggested that the threshold for investigating AI should be low because of the limitations of physical examination, particularly in patients with septic shock.

What test should be included in routine weaning profiles is still controversial. Manthous and coworkers (30) suggested that most currently used weaning parameters are better at identifying still controversial. Manthous and coworkers (30) suggested that physical examination, particularly in patients with septic shock.

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succeed with spontaneous breathing. Shikora and coworkers (31) noted that patients meeting accepted predictive work of breathing criteria frequently require reintubation within 48 h of extubation. Correcting AI may prove an ideal measure of VW.

### Conclusions

In conclusion, AI should be suspected in the critically ill when morning cortisol concentrations are lower than 25 μg/dl, and this can be confirmed if cortisol increments are less than 9 μg/dl with ACTH stimulation testing. Evaluation of AI is recommended for all patients before extubation since stress dose corticosteroid supplementation in patients with AI can improve the chances of successful VW, shortening the duration of weaning such that patients with AI are comparable with patients with adequate adrenal reserves.

### Conflict of Interest Statement

Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

### Acknowledgment

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### References


