# Assessment of the effect of continuous sedation with mechanical ventilation on adrenal insufficiency in patients with traumatic brain injury

Min Li, Ying Zhang, Kang-Song Wu, Ying-Hong Hu

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jim-2015-000012).

Neurointensive Care Unit, The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China

**Correspondence to**
Dr Ying-Hong Hu, Neurointensive Care Unit, The Second Affiliated Hospital Zhejiang University School of Medicine, No. 88 Jiefang Road, Hangzhou 310009, Zhejiang Province, China; 2504188@zju.edu.cn

Accepted 6 January 2016
Published Online First 10 February 2016



## ABSTRACT

The aim of this study was to assess the effect of continuous propofol sedation plus prolonged mechanical ventilation on adrenal insufficiency (AI) in patients with traumatic brain injury (TBI). Eighty-five adult patients diagnosed with moderate TBI (Glasgow Coma Scale (GCS) score 9–13) from October 2011 to October 2012 were included in this prospective study. The patients comprised three groups: no mechanical ventilation and sedation (n=27), mechanical ventilation alone (n=24) and mechanical ventilation plus sedation (n=34). The low-dose short Synacthen test was performed at 8:00 on the first, third, and fifth days after TBI. Logistic regression analysis was performed to identify factors affecting the use of mechanical ventilation and sedation, and the incidence of AI. On the fifth day after injury, the mean baseline cortisol and simulated cortisol levels were significantly lower in the mechanical ventilation plus sedation group compared with the other two groups. Multivariate regression analysis showed that the Acute Physiology and Chronic Health Evaluation (APACHE) score was independently associated with treatment with mechanical ventilation and sedation compared to mechanical ventilation alone. Furthermore, hypoxemia on admission and shock were associated with the development of AI. The findings showed that sedation is associated with an increased incidence of AI. Patients with TBI who are treated with continuous sedation should be monitored for AI carefully.

### Significance of this study

**What is already known about this subject?**

- Traumatic brain injury (TBI) followed by neuroendocrine dysfunction is well known.
- Patients with TBI who had adrenal insufficiency (AI) remain a clinical challenge.
- The effect of some sedatives on the adrenal function is still controversial.

**What are the new findings?**

- The Acute Physiology and Chronic Health Evaluation (APACHE) score was associated with treatment with mechanical ventilation and sedation.
- Hypoxemia and shock were associated with the development of AI.
- Sedation is associated with an increased incidence of AI.

**How might these results change the focus of research or clinical practice?**

- The low-dose stimulation test may be a good test for secondary AI in the acute setting. Patients with TBI who are treated with continuous sedation should be monitored carefully for AI.

## INTRODUCTION

When traumatic brain injury (TBI) occurs, several hormones related to stress are released.[1] However, in many instances, TBI is followed by neuroendocrine dysfunction and in recent years this has become recognized as an important complication of TBI.[2 3] Most often, changes in the hypothalamic-pituitary-adrenal (HPA) axis are involved in neuroendocrine dysfunction after TBI.[1]

Cohan *et al*[4] reported that approximately one-half of the patients with moderate or severe TBI have adrenal insufficiency (AI), at least temporarily. Similarly, Dupuis *et al*[5] reported that 36% of pediatric patients with TBI have secondary AI. Since it can be life-threatening, AI in the acute phase of TBI has received special attention.[6 7] Left untreated, the result can be hemodynamic instability and a poor outcome.[4] Even though glucocorticoid replacement therapy has been used for more than 60 years, managing patients with AI remains a clinical challenge.[7] Also, it is important that AI be correctly diagnosed because giving corticosteroids unnecessarily to patients in a critical condition with neurological damage can adversely affect their clinical course.[8]

Both greater injury severity and prolonged mechanical ventilation are considered to be related to AI early after TBI.[5 9] Usually, patients with severe TBI have tracheal intubations and their lungs mechanically ventilated to avoid

**To cite:** Li M, Zhang Y, Wu K-S, *et al*. *J Investig Med* 2016;**64**:752–758.

hypoxemia.[10] Sedation may be provided to reduce anxiety or agitation, resolve patient-ventilator dyssynchrony, and manage raised intracranial pressure (ICP) in patients with TBI.[11] However, the results of a study by Kollef *et al*[12] suggest that there may be an association between continuous intravenous sedation and prolonged need for mechanical ventilation. The effect of some sedatives on the adrenal function of critically ill patients has been controversial since a report in 1983 by Ledingham and Watt.[13] It is known that a neuroendocrine dysfunction in ventilated patients can complicate the weaning process. Using high-dose propofol and pentobarbital has been reported to be significantly associated with AI.[4] Moreover, Skoglund *et al*[1] reported that the interruption of continuous sedation to perform the 'neurological wake-up test' can induce a stress response with increased cortisol levels in patients on mechanical ventilation.

Therefore, the purpose of this prospective study was to assess the effect of continuous propofol sedation plus prolonged mechanical ventilation on AI in patients with TBI.

## MATERIALS AND METHODS

The hospital research ethics committee granted study protocol approval and the patients' relatives gave their written informed consent for this study.

### Participants

Patients with a diagnosis of moderate TBI (Glasgow Coma Scale (GCS) score 9–13) admitted to our neurointensive care unit (ICU) from October 2011 to October 2012 were recruited for this prospective cohort study. The exclusion criteria were: Addison disease, pituitary adenoma confirmed by pituitary MRI, diabetes, severe infection, treatment with corticosteroid or etomidate therapy following TBI, and pregnant or lactating. There were 85 patients included in the final analysis. All included patients had Richmond Agitation-Sedation Scale (RASS) scores of −2 to 0[14] and comprised three groups: no mechanical ventilation and sedation, mechanical ventilation alone and mechanical ventilation plus sedation. Propofol was the only sedative administered when sedation was needed.

The following data were collected: age, sex, operation, GCS on admission, Acute Physiology and Chronic Health Evaluation II score (APACHE-II) on admission, duration of continuous sedation, ICU length of stay, duration of mechanical ventilation, and mean arterial pressure (MAP).

The critical-care pain observation tool (CPOT) was used to evaluate pain. Patients with CPOT scores of ≥4 were given analgesia treatment with fentanyl. Analgesic drugs were given so that the CPOT score was reduced to <4. After satisfactory analgesia, we used the RASS score to evaluate whether continuous sedation was required or not and gave the sedative drugs to make the RASS score −2 to 0 points. If the score was <−2 points, we reduced the dose of sedative drugs or stopped medication; if the score was >0, we increased the dose of sedative drugs.

After admission, patients were treated with endotracheal intubation and mechanical ventilation, or both plus sedation or were not treated with any of these three methods according to the state of consciousness, respiratory status, sputum expectoration ability, blood gas analysis results and evaluation of restlessness after mechanical ventilation. The indications for endotracheal intubation were as follows: (1) severe hypoxemia or hypercapnia requiring a relatively long time for mechanical ventilation; (2) cannot expectorate the upper respiratory tract secretions, gastric reflux or blood autonomously, and there is a risk of aspiration; (3) excessive lower respiratory tract secretions or bleeding, and the ability of independent expectoration is relatively poor; (4) respiratory tract injury, stenosis, obstruction, etc, which may seriously affect the normal respiration; and (5) a sudden respiratory arrest requiring urgent establishment of an artificial airway for mechanical ventilation. The indications for mechanical ventilation were as follows: unconsciousness; severely abnormal respiratory patterns, such as respiratory rate >35–40/min or <6–8/min; abnormalities in respiratory rhythm, reduced or absent spontaneous breathing, etc.; severe ventilation and/or oxygenation disorders shown by blood gas analysis $PaO_2$ <50 mm Hg, especially after sufficient oxygenotherapy; and progressive increase of $PaCO_2$ and dynamic decrease of pH. Hypoxemia was defined as either 'oxygen pressure' (arterial) $PaO_2$ <60 mm Hg or 'oxygen saturation' (arterial) $SaO_2$ <90%.

### Samples

Morning blood samples to measure baseline cortisol and adrenocorticotropic hormone (ACTH) levels were collected at 8:00 on the first, third and fifth days after injury onset. Blood samples were obtained 30 and 60 min after a bolus injection of 1 μg of corticotropin (Synacthen, Novartis, Basel, Switzerland) to perform the low-dose short Synacthen test (LDSST). AI was defined as non-response to the LDSST in conjunction with stimulated peak cortisol concentrations of <500 nmol/L.[15]

### Analysis

Blood samples were first collected in EDTA-coated tubes to assay plasma ACTH using immunochemiluminescence (E170, Roche, Basel, Switzerland) and in glass tubes without anticoagulant to assay serum cortisol using immunochemiluminescence (Immulite 2000, DPC, Los Angeles, California, USA), and then immediately transported to the laboratory for measurement. Normal values in non-stressed individuals are 7.2–63.3 pg/mL for plasma ACTH and 154.0–638.0 nmol/L for serum cortisol.

### Statistical analysis

Continuous variables were presented as means and SDs. A one-way ANOVA with Bonferroni post hoc tests was used to compare the differences between different groups of mechanical ventilation and sedation. Categorical variables were presented together as counts and percentages. $\chi^2$ Tests or Fisher's exact tests were appropriately used for group comparisons. Univariate and multivariate multinomial logistic regression models were performed to identify the factors associated with different types of mechanical ventilation and sedation treatments (ie, mechanical ventilation alone, mechanical ventilation and sedation, no mechanical ventilation and sedation) and to identify factors affecting the incidence of AI. Variables which reached statistical significance or had clinical meaning in each univariate model were included in the multivariate model. Statistical analysis was considered significant at the two-sided p value <0.05. The statistical

analyses were performed by using IBM SPSS statistical software V.22 (IBM Corp., Armonk, New York, USA).

## RESULTS

### Characteristics of patients

A total of 85 patients were included in this study, 56 males and 29 females; their mean age was 46.4 years. In all patients, the duration of TBI events was the same; however, their total time of stay in the ICU differed. The demographic and clinical characteristics of the patients are presented in table 1. The mean APACHE) score was significantly higher in the mechanical ventilation alone group compared with the no mechanical ventilation and sedation group (20.92 vs 18.11, p=0.01). The incidence of hypoxemia, shock and AI were all higher in the mechanical ventilation plus sedation group than in the other two groups (all p ≤0.039) (table 1).

### Comparisons of cortisol, ACTH, mechanical ventilation time, and AI

Comparisons of cortisol, ACTH levels, mechanical ventilation time, and AI among the three groups at one, three, and 5 days after injury are presented in table 2. There were no significant differences among the groups at 1 and 3 days after injury in cortisol, ACTH levels, mechanical ventilation time, or AI (all p>0.05). On the fifth day after injury, the mean baseline cortisol and stimulated cortisol levels were significantly lower in the mechanical ventilation plus sedation group compared with the other two groups (baseline cortisol: 449.15 vs 598.74, 566.92 nmol/L, p≤0.014; stimulated cortisol: 551.3 vs 685.8, 711.21 nmol/L, p≤0.001). The mean ACTH level was significantly lower in the mechanical ventilation alone and mechanical ventilation plus sedation groups compared with the no mechanical ventilation and sedation group (20.1 and 18.98 vs 35.5 pg/mL, p≤0.01) (table 2).

### Results of logistic regression analysis to identify factors affecting different types of treatment

The results of univariate and multivariate models showed that the APACHE score on admission was a significant factor affecting treatment with mechanical ventilation alone compared with no mechanical ventilation and sedation. The odds of mechanical ventilation alone were significantly increased compared with no mechanical ventilation and sedation with the APACHE score increased (in univariate model: OR=1.3, p=0.005; in multivariate model: OR=1.33, p=0.003) (model 1, table 3).

The results of univariate models showed that hypoxemia on admission, AI and shock were factors significantly affecting mechanical ventilation plus sedation compared with no mechanical ventilation and sedation. The odds of treatment with the mechanical ventilation plus sedation group were significantly increased compared with no

**Table 1** Characteristics of patients

| | Mechanical ventilation and sedation | | | |
|---|---|---|---|---|
| | No mechanical ventilation and sedation (N=27) | Mechanical ventilation alone (N=24) | Mechanical ventilation plus sedation (N=34) | p value |
| Age (years) | 47.78±16.29 | 43.71±15.32 | 47.21±17.26 | 0.634 |
| Gender | | | | 0.825 |
| Male | 17 (30.36%) | 17 (30.36%) | 22 (39.29%) | |
| Female | 10 (34.48%) | 7 (24.14%) | 12 (41.38%) | |
| APACHE score (admission) | 18.11±2.64 | 20.92±3.62* | 19.47±3.54 | 0.013† |
| Albumin (admission) | 33.01±3.43 | 32.2±3.16 | 32.36±2.85 | 0.605 |
| GCS (admission) | 10.11±1.28 | 10.33±1.31 | 10.12±1.25 | 0.777 |
| Hypoxemia (admission) | 2 (14.29%) | 2 (14.29%) | 10 (71.43%) | 0.039† |
| Operation | 5 (18.52%) | 8 (29.63%) | 14 (51.85%) | 0.165 |
| Mortality | 0 (0%) | 1 (25%) | 3 (75%) | 0.300 |
| Type of TBI | | | | 0.787 |
| Epidural hematoma | 9 (40.91%) | 5 (22.73%) | 8 (36.36%) | |
| Subdural hematoma | 8 (27.59%) | 11 (37.93%) | 10 (34.48%) | |
| Intracerebral hematoma plus cerebral contusion | 6 (27.27%) | 6 (27.27%) | 10 (45.45%) | |
| Diffuse axonal injury | 4 (33.33%) | 2 (16.67%) | 6 (50%) | |
| Mechanical ventilation time (h) | | | | 0.169 |
| <24 | – | 5 (71.43%) | 2 (28.57%) | |
| 24–48 | – | 4 (30.77%) | 9 (69.23%) | |
| 48–72 | – | 8 (53.33%) | 7 (46.67%) | |
| >72 | – | 7 (30.43%) | 16 (69.57%) | |
| Mean arterial pressure during the hospital stay (mm Hg) | 85.04±14.15 | 87.36±13.58 | 80.29±11.65 | 0.112 |
| Incidence of shock | 2 (11.76%) | 2 (11.76%) | 13 (76.47%) | 0.003† |
| Usage of norepinephrine | 2 (33.33%) | 1 (16.67%) | 3 (50%) | 0.876 |
| Adrenal insufficiency | 3 (15%) | 4 (20%) | 13 (65%) | 0.030† |

*p<0.05, indicates significant difference compared with the no mechanical ventilation and sedation group.
†p<0.05, indicates significant difference between different treatment groups.
APACHE, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

**Table 2** Comparisons of cortisol, ACTH, mechanical ventilation time, and adrenal insufficiency

| | Mechanical ventilation and sedation | | | |
|---|---|---|---|---|
| | No mechanical ventilation and sedation (N=27) | Mechanical ventilation alone (N=24) | Mechanical ventilation plus sedation (N=34) | p value |
| First day after injury | | | | |
| Baseline cortisol (nmol/L) | 634.81±238.15 | 633.05±182.07 | 548.35±169.64 | 0.152 |
| Stimulated cortisol (nmol/L) | 722.04±164.28 | 718.29±157.96 | 645.63±142.34 | 0.097 |
| ACTH (pg/mL) | 27.13±15.17 | 23.39±12.41 | 26.99±12.82 | 0.534 |
| Mechanical ventilation time (h) | – | 16.96±4.87 | 15.22±6.94 | 0.296 |
| Adrenal insufficiency | 1 (20%) | 2 (40%) | 2 (40%) | 0.856 |
| Third day after injury | | | | |
| Baseline cortisol (nmol/L) | 684.53±241.79 | 635.88±192.86 | 566.36±191.99 | 0.092 |
| Stimulated cortisol (nmol/L) | 657.55±208.62 | 599.18±108.03 | 615.36±197.86 | 0.487 |
| ACTH (pg/mL) | 29.08±15.78 | 28.18±19.21 | 24.62±13.71 | 0.517 |
| Mechanical ventilation time (h) | – | 48.19±17.87 | 53.01±15.54 | 0.278 |
| Adrenal insufficiency | 3 (30%) | 3 (30%) | 4 (40%) | 1.000 |
| Fifth day after injury | | | | |
| Baseline cortisol (nmol/L) | 598.74±143.38 | 566.92±156.47 | 449.15±153.81*† | 0.001‡ |
| Stimulated cortisol (nmol/L) | 685.8±157.56 | 711.21±126.72 | 551.3±130.31*† | <0.001‡ |
| ACTH (pg/mL) | 35.5±27.2 | 20.1±9.44* | 18.98±13.4* | 0.001‡ |
| Mechanical ventilation time (h) | – | 54.5±25.76 | 66.51±26.98 | 0.094 |
| Adrenal insufficiency | 1 (7.14%) | 0 (0%) | 13 (92.86%) | <0.001‡ |

*p<0.05, indicates significant difference compared with the no mechanical ventilation and sedation group.
†p<0.05, indicates significant difference compared with the mechanical ventilation alone group.
‡p<0.05, indicates significant difference between different treatment groups.

mechanical ventilation and sedation for patients with hypoxemia on admission, AI, or shock (hypoxemia on admission: OR=5.21, p=0.046; AI: OR=4.95, p=0.024; shock: OR=7.74, p=0.012).

There were no significant findings in the multivariate model 2 (p>0.05) (table 3).

The results of univariate models showed that MAP during the hospital stay and incidence of shock were significant factors affecting treatment with the mechanical ventilation plus sedation group compared with mechanical ventilation alone. The odds of mechanical ventilation plus sedation were significantly decreased compared with mechanical ventilation alone with an increased MAP during the hospital stay (OR=0.96, p=0.047), as well as significantly increased compared with mechanical ventilation alone for patients with shock (OR=6.81, p=0.019).

After adjustment for the other factors, the odds of mechanical ventilation plus sedation were significantly decreased compared with mechanical ventilation alone with an increased APACHE score (OR=0.82, p=0.034) (model 3, table 3).

### Results of logistic regression analysis to identify factors affecting the incidence of AI

Among the 85 patients, 20 had AI and 65 did not. Variables that significantly affected AI incidence in univariate analysis were included in the multivariate model (see online supplementary table). After adjustment for gender, sedation time, shock, and norepinephrine, the odds of AI incidence were significantly increased in patients with hypoxemia on admission compared with patients without hypoxemia on admission (OR=20.43, p=0.033). The odds of AI incidence were significantly increased in patients with shock compared with patients without shock (OR=17.87, p=0.032).

## DISCUSSION

Our study compared the effect of continuous sedation using propofol with mechanical ventilation with regard to the incidence of AI in patients with TBI. We found that on the fifth day after injury the mean baseline cortisol and stimulated cortisol levels were significantly lower in the mechanical ventilation plus sedation group compared with the no mechanical ventilation and sedation group and the mechanical ventilation alone group and that the mean ACTH level was significantly lower in the mechanical ventilation group alone and the mechanical ventilation plus sedation group compared with the no mechanical ventilation and sedation group. We also found that hypoxemia on admission and incidence of shock were significant independent factors for increased incidence of AI. Mechanical ventilation plus sedation was a significant factor in univariate analysis but not in the multivariate model.

Propofol sedation has a favorable safety profile and is known to be safe for patients being treated with mechanical ventilation, but it may prolong mechanical ventilation and impair cognitive function.[12 16] The pharmacokinetic characteristics of propofol include rapid distribution and rapid elimination. During the early phase of sedation, cortisol levels but not ACTH levels decrease. It is likely that sedative drugs mitigate the general stress response.[17]

Schricker *et al*[18] were the first to report that a decrease in plasma cortisol concentration 90 min after anesthesia was induced by single-dose propofol. Morel *et al*[19] carried out a double-blind randomized study of the hemodynamic effects of administering etomidate to induce anesthesia in

**Table 3** Results of logistic regression analysis to identify factors affecting different types of mechanical ventilation and sedation

| | Univariate model | | Multivariate model | |
|---|---|---|---|---|
| | OR (95% CI) | p value | OR (95% CI) | p value |
| Model 1-Mechanical ventilation alone vs unused | | | | |
| Age (years) | 0.98 (0.95 to 1.02) | 0.374 | | |
| Gender (ref=female) | 1.43 (0.44 to 4.63) | 0.552 | | |
| Type of TBI (ref=epidural hematoma) | | | | |
| Subdural hematoma | 2.48 (0.6 to 10.27) | 0.212 | | |
| Intracerebral hematoma plus cerebral contusion | 1.8 (0.37 to 8.68) | 0.464 | | |
| Diffuse axonal injury | 0.9 (0.12 to 6.78) | 0.919 | | |
| Hypoxemia on admission (ref=no) | 1.14 (0.15 to 8.76) | 0.902 | 0.66 (0.07 to 6.11) | 0.717 |
| Operation(ref=no) | 2.2 (0.61 to 7.99) | 0.231 | | |
| APACHE (on admission) | 1.3 (1.08 to 1.56) | 0.005* | 1.33 (1.1 to 1.61) | 0.003* |
| Albumin (on admission) | 0.92 (0.77 to 1.1) | 0.358 | | |
| GCS (on admission) | 1.15 (0.74 to 1.76) | 0.537 | | |
| Mean arterial pressure during the hospital stay (mm Hg) | 1.01 (0.97 to 1.06) | 0.525 | 1.03 (0.98 to 1.09) | 0.264 |
| Adrenal insufficiency (ref=no) | 1.6 (0.32 to 8.01) | 0.567 | 1.59 (0.23 to 10.77) | 0.636 |
| Incidence of shock (ref=no) | 1.14 (0.15 to 8.76) | 0.902 | 1.16 (0.09 to 15.43) | 0.912 |
| Model 2-Mechanical ventilation plus sedation vs unused | | | | |
| Age (years) | 0.998 (0.97 to 1.03) | 0.890 | | |
| Gender (ref=female) | 1.08 (0.38 to 3.09) | 0.888 | | |
| Type of TBI (ref= epidural hematoma) | | | | |
| Subdural hematoma | 1.41 (0.37 to 5.32) | 0.616 | | |
| Intracerebral hematoma plus cerebral contusion | 1.88 (0.47 to 7.53) | 0.375 | | |
| Diffuse axonal injury | 1.69 (0.35 to 8.22) | 0.517 | | |
| Hypoxemia on admission (ref=no) | 5.21 (1.03 to 26.27) | 0.046* | 2.99 (0.48 to 18.76) | 0.243 |
| Operation(ref=no) | 3.08 (0.94 to 10.1) | 0.063 | | |
| APACHE (on admission) | 1.14 (0.97 to 1.35) | 0.110 | 1.1 (0.92 to 1.3) | 0.297 |
| Albumin (on admission) | 0.93 (0.79 to 1.1) | 0.416 | | |
| GCS (on admission) | 1.004 (0.66 to 1.52) | 0.983 | | |
| Mean arterial pressure during the hospital stay (mm Hg) | 0.97 (0.93 to 1.01) | 0.159 | 1.002 (0.95 to 1.05) | 0.944 |
| Adrenal insufficiency (ref=no) | 4.95 (1.24 to 19.79) | 0.024* | 1.62 (0.29 to 9.03) | 0.583 |
| Incidence of shock (ref=no) | 7.74 (1.57 to 38.24) | 0.012* | 5.05 (0.65 to 39.1) | 0.121 |
| Model 3-Mechanical ventilation plus sedation vs mechanical ventilation alone | | | | |
| Age (years) | 1.01 (0.98 to 1.05) | 0.421 | | |
| Gender (ref=female) | 0.75 (0.24 to 2.33) | 0.625 | | |
| Type of TBI (ref= epidural hematoma) | | | | |
| Subdural hematoma | 0.57 (0.14 to 2.32) | 0.431 | | |
| Intracerebral hematoma plus cerebral contusion | 1.04 (0.23 to 4.7) | 0.958 | | |
| Diffuse axonal injury | 1.87 (0.27 to 13.2) | 0.528 | | |
| Hypoxemia on admission (ref=no) | 4.58 (0.9 to 23.27) | 0.066 | 4.51 (0.73 to 27.8) | 0.105 |
| Operation(ref=no) | 1.4 (0.47 to 4.16) | 0.545 | | |
| APACHE (on admission) | 0.88 (0.75 to 1.03) | 0.116 | 0.82 (0.69 to 0.99) | 0.034* |
| Albumin (on admission) | 1.02 (0.85 to 1.21) | 0.850 | | |
| GCS (on admission) | 0.88 (0.58 to 1.32) | 0.527 | | |
| Mean arterial pressure during the hospital stay (mm Hg) | 0.96 (0.92 to 0.9994) | 0.047* | 0.97 (0.92 to 1.03) | 0.297 |
| Adrenal insufficiency (ref=no) | 3.1 (0.86 to 11.1) | 0.083 | 1.02 (0.19 to 5.59) | 0.983 |
| Incidence of shock (ref=no) | 6.81 (1.37 to 33.87) | 0.019* | 4.36 (0.48 to 39.91) | 0.192 |

*p<0.05, indicates significantly associated with the mechanical ventilation alone group or mechanical ventilation plus sedation group.
APACHE, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.
The term "ref" denotes the reference category of the categorical variables for the odds ratio estimation.

patients undergoing elective cardiac surgery and administered propofol to the control group. A short corticotropin (tetracosactide (250 μg)) stimulation test was performed and relative AI was measured.[19] Relative AI has only recently become accepted as a diagnosis and it is based on the concept that in patients who are critically ill an elevated cortisol level may be inadequate.[20] Morel *et al*[19] found that, using their definition of AI, approximately 40% and 25% of patients had relative AI at 12 and 24 h after etomidatel administration, respectively. Lindgren *et al*[8] assessed critical illness-related corticosteroid insufficiency in the acute phase after subarachnoid hemorrhage (SAH) and found that continuous intravenous sedation was significantly associated with cortisol values under defined limits

and that levels of morning serum cortisol at 96 h after SAH were lowest in sedated patients. We used propofol alone for continuous sedation, whereas the patients with SAH in the study by Lindgren *et al* were continuously sedated with propofol alone or in combination with thiopental and midazolam and their morning serum cortisol levels were not significantly associated with the various sedative drugs. Though the ACTH and corticotropin stimulation tests were not used in the study by Lindgren *et al*, we speculate that the AI found in both their study and our study was due to the same mechanism, that is, inhibition of the HPA axis.

Although the sedative dose was low in unit time, sustained application reduced the response to exogenous stress and also inhibited the release of cortisol. Thus, the cortisol in the circulation was reduced. After use of similar sedatives during anesthesia, the cortisol in the blood collected in the morning of the second day was found to be reduced. ACTH at physiological concentration usually fails to normalize cortisol soon after discontinuation of sedative treatment. Thus, in patients positive for LDST at physiological concentration, cortisol is often insufficient, and such patients may develop secondary AI after sedation. However, this type of secondary AI is transient and may resolve over time. In patients with severe TBI, the secondary AI usually lasts for several months or even several years, which might be related to the reduced synthesis of cortisol. Thus, our results are helpful for differentiating secondary AI in the early phase of TBI.

In the AI group, a higher proportion of patients had aspiration pneumonia, and therefore a greater percentage had hypoxemia than in the non-AI group. Also, a higher proportion of patients in the AI group at admission had shock, which is known to be a major factor that might lead to AI.

In this study, the septic shock and hypoxemia in included patients were related to inspiration pneumonia due to vomiting after TBI. All these patients received mechanical ventilation and sedation due to the early respiratory distress. Thus, these patients were included in the mechanical ventilation plus sedation group. Univariate analysis showed that AI was a risk factor. In these patients, the respiratory distress was recovered in some patients, short-term use of sedatives was employed, and the incidence of secondary AI was low. Thus, these parameters were excluded from the multivariate analysis. Although septic shock was a risk factor of AI, it often observed in patients with severe sepsis whose septic shock could not be improved by increasing blood volume and use of vasoactive drugs (US guideline for the therapy of sepsis in 2012). The univariate analysis is for each 'single' variable to make an individual analysis in the model. For the multivariate analysis, all variables were put together into the model and analyzed at the same time. If the statistical significance of an individual variable is not enough to continue, those specific variables may lose statistical significance in multivariate analysis.

Patients with mechanical ventilation plus sedation tended to have more intracerebral hematomas and diffuse axonal injuries in addition to increased hypoxemia. In patients with intracerebral hematoma and diffuse axonal injury, the GCS score was higher than 8 in the early phase. Patients with severe TBI received intubation in the early phase, and therefore early intratracheal intubation was not feasible. This causes a high incidence of aspiration, which in turn causes hypoxemia.[21 22]

For this study, we used the low-dose ACTH stimulation test which was performed by administering a bolus inject of 1 μ of corticotropin. In many studies, the standard 250 μg dose has been used. Whether one of these ACTH stimulation test doses is superior to the other or whether they are comparable remains unclear. Kazlauskaite *et al*[23] reviewed the literature from 1966 to 2006 and found that the low-dose corticotropin test was superior to the standard dose test. In a study by Dekkers *et al*,[24] in which low-dose and standard dose tests were directly compared, the investigators found that the tests produced comparable results. However, they noted that the tests can produce different results in individual patients. On the basis of this information comparing doses, we believe that our use of the low dose was appropriate for this study.

This study had several limitations. First, this was a single-centre short-term study with a small sample size. In future multicentre studies, the sample size should be increased. Second, we included only those patients with moderate brain injury (GCS score 9–13) in our analysis because severe brain damage can cause AI.[25] Third, we limited our study to patients sedated by propofol, so our results are not directly applicable to patients sedated with other sedatives. We also think that the results of the odds of AI incidence were significantly increased in male patients due to selection bias (table 1). We did not intentionally make such a selection bias. However, the gender bias may affect the interpretations of results. It is of note that there is worse hypoxemia and sepsis in the propofol sedation group, which are most likely simply other markers of illness severity. More patients in shock and more patients requiring vasopressor support were present in the mechanical ventilation and sedation cohort, which suggests a difference between the groups in terms of the neurological injury. We did not use the metyropone test or insulin tolerance test (ITT), even though these tests are highly accurate for evaluation of AI. The metyropone test is associated with several side effects such a nausea, vomiting, and dizziness, and can even cause an adrenal crisis Therefore, the metyropone test is not used that often in clinical practice. The ITT is associated with a risk of severe hypoglycemia and can even pose a risk to life in critically ill patients and therefore is not feasible. We did not investigate circulating cytokine levels to elucidate the role of mechanical ventilation-induced cytokines release. Furthermore, the role of activation of afferent fibers of the autonomic nervous system could be explored in experiments with pharmacological or surgical manipulations of the noradrenergic and vagus systems. Grap *et al*[26] had suggested that the level of sedation most likely does not affect the stability of physiological status but does have an effect on comfort. However, we cannot provide explanations for the data on severity of patients measured with APACHE and need of mechanical ventilation and sedation. Finally, although we obtained data on other pituitary hormones in addition to ACTH after TBI, including thyroid-stimulating hormone, prolactin, follicle stimulating hormone, luteinizing hormone, and growth hormone, we did not include these data in order to keep the focus of the study on ACTH and cortisol.

## CONCLUSIONS

Our results show that there is an association between mechanical ventilation plus sedation and the incidence of AI. The finding suggests that patients with TBI who are treated with continuous sedation should be monitored for AI.

**Funding** The authors declare that they have received research grants from Zhejiang Province Medical and Health Research Foundation (project number: 2010KYA098).

**Competing interests** None declared.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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