Electroacupuncture reduces the dose of midazolam monitored by the bispectral index in critically ill patients with mechanical ventilation: an exploratory study

Xia Zheng,1 Jian-biao Meng,2 Qiang Fang1

ABSTRACT

Objective Electroacupuncture, a modern variation on a traditional Chinese treatment, might be useful for sedation and analgesia. This study aims to investigate whether electroacupuncture can modify the dose of midazolam monitored by the bispectral index (BIS) in critically ill patients with mechanical ventilation.

Methods Orotracheally intubated patients undergoing mechanical ventilation were randomly assigned into three groups (groups A, B and C). All patients were given an intravenous infusion of midazolam. Patients in group A received no additional treatment. Patients in group B were given acupuncture without electrical stimulation at acupuncture points GV24 and EX–HN3 (Yintang) for 6 h simultaneously, and patients in group C were given electroacupuncture to the same points as in group B.

Results Maintaining the BIS between 60 and 80, the hourly mean one dose of midazolam within the first 6 h after sedation in group C was 0.05 (±0.02 mg/kg per hour), which was significantly lower than both group A (0.08±0.03 mg/kg per hour, p<0.001) and group B (0.07±0.01 mg/kg per hour, p<0.021). The doses in groups A and B showed no significant difference. Between-group comparison analysis of hepatic and renal function and severe adverse reactions all showed no significant difference between the three groups.

Conclusions Electroacupuncture appears to reduce markedly the dose of sedative drug required in critically ill patients with mechanical ventilation monitored by BIS, without any obvious severe adverse action, and larger studies to confirm the effect are justified.

Critically ill patients in intensive care units (ICU) are on life-support systems (mechanical ventilation, blood purification, etc), away from their family and familiar surroundings. Due to the influences of various social and environmental factors, some of these patients may develop emotional disorders, such as anxiety, tension, fear, loneliness, insomnia, irritability, loss of self-control and other emotional and mental disorders. They may even become uncooperative with their healthcare providers. These emotional disorders may even persist after discharge from intensive care.1 These stresses often lead to body metabolism disorders and tissue damage, which clinical monitoring and treatment measures often fail to control.2,3 Therefore, for such critically ill patients, it is essential to achieve the appropriate degree of sedation to control the metabolic rate and oxygen consumption,4 and reduce a range of stress and inflammatory injuries5 and even organ damage.

A study of admissions over 28 days to 361 ICU in different countries showed that approximately one-third of patients needed mechanical ventilation in the ICU for a mean duration of 5.9 days (SD 7.2).6 It is well known that mechanical ventilation patients need to receive adequate analgesia and sedation because of painful or uncomfortable experiences in the course of treatment.7,8 At present, the main method of sedation is pharmacological. However, in practice, various adverse effects of sedative drugs, for example nausea, respiratory depression, hypotension, tachycardia, bradycardia, or arrhythmias, occur and require to be minimised. Close monitoring and attention to the sedation status of patients on mechanical ventilation is very important. The bispectral index (BIS) is a specific analysis of the EEG variations that correspond to different levels of sedation – anaesthesia, awakening and coma.9 When a patient is awake, the cerebral cortex is very active, and the EEG reflects vigorous activity. When a patient is asleep or under general anaesthesia, the pattern of EEG activity changes. Overall, there is a change from higher frequency signals to lower frequency signals. The essence of BIS is to take a complex signal (the EEG), analyse it, and process the result as a single number. BIS is a weighted sum of EEG subparameters, including a time domain, frequency domain and high order spectral subparameters.10 The BIS monitor provides a single dimensionless number, which ranges from 0 (equivalent to EEG silence) to 100 (equivalent to fully awake and alert). BIS can effectively guide the regulation of the depth of sedation in the ICU.11,12
As a therapy complementary to opioid analgesics for pain relief during or after procedures including surgery, acupuncture can partly reduce opioid-related side effects. Until now, studies of acupuncture usually focused on its analgesic effect. For example, during shockwave lithotripsy and colonoscopy, acupuncture may decrease the demand for sedative drugs partly because of analgesia. There are few, if any, reports on the combined sedative effect of electroacupuncture and a sedative drug (midazolam), especially in critically ill patients during mechanical ventilation monitored by BIS. Therefore, the present study is designed to explore whether the sedative effect of electroacupuncture at GV24 (Shenting) and EX–HN3 (Yintang) can influence the dose of midazolam and reduce the risks of multiple organ dysfunction and other side effects of the sedative drug.

METHODS
The study was approved by the Human Investigation Committee at the Medical College of Zhejiang University. All informed consents were provided by family members. In our ICU, orotracheal intubated patients with mechanical ventilation, who were more than 18 years of age, and needed sedation for more than 6 h, were enrolled in the study. The exclusion criteria were as follows: patients with a history of mental disease or who need to take other types of psychotropic drugs, which may cause difficulty in evaluating sedation; patients who cannot be assessed due to coma; patients who have severe liver or kidney function disorders, leading to possible drug accumulation; patients with a known allergy to benzodiazepines; patients with severe, irreversible low blood pressure, ie, systolic blood pressure below 90 mm Hg before the use of midazolam, even with a vasopressor drug; patients whose heart rate is less than 50 beats per minute before the use of midazolam; patients with myasthenia gravis; patients who have a history of substance abuse; patients who are obese, defined as twice the ideal body weight; pregnancy. The patients’ progress is shown in the flow chart (figure 1).

**Figure 1**  Flow chart of the patients through the trial.

To assign patients randomly a series of 45 random numbers was generated from random numbers tables and converted into three groups. To achieve a balanced design, we arranged the 45 numbers into three equal groups of 15. Papers marked with the group allocation (A, B or C) were placed in 45 numbered sealed, opaque envelopes. Following completion of enrolment, a research assistant opened the envelope to assign a study group to the participant.

Intravenous injection of midazolam alone was given to patients in group A. To patients in group B, midazolam was given and acupuncture needles (filiform needles made of stainless steel) were applied to acupuncture points at GV24 and Yintang for 6 h simultaneously. The needles were manipulated by reinforced lift and thrusting to elicit Qi, then the needles remained in situ for 6 h. To patients in group C, midazolam was given and electroacupuncture was given using needles inserted as in group B (figure 2). A Han’s acupoint nerve stimulator type LH 202 was connected. The parameters of electroacupuncture stimulation were as follows: 3-s bursts alternating between 2 Hz and 100 Hz, at 10–15 mA intensity inducing no discomfort, without muscle contraction. Electrical stimulation was maintained for 30 min alternating with periods of rest for 30 min, repeated six times until the end of the experiment. Chinese medicine practitioners in our hospital were responsible for the whole acupuncture process.

All selected patients were in a sober state, with oral intubation during mechanical ventilation with a Drager-Evita 4 ventilator (in biphasic positive airway pressure/assist mode; Drager Medical AG & Co., Lubeck, Germany), and a PritanBennett-840 ventilator (in assist/control–pressure control mode; Boulder, CO, USA). BIS (Aspect Medical Systems, MA, USA) were monitored with a German Philips monitor MP70/80 (Philips Medizin Systeme Boeblingen GmbH, Boeblingen, Germany) (see figure 2). Acupuncture needles were placed in the acupuncture points at GV24 and Yintang in groups B and C. The acupuncture needles (Ace Acupuncture Supplies, China Town, New York, USA) (diameter×length: 0.25 mm×40 mm) in GV24 were inserted an inch directed towards GV20 (Baihui), and in Yintang half an inch directed towards the nose tip. First, all selected patients were awake. This was assessed as
responding to command, voluntary movement of both upper and lower limbs, cooperation, and a BIS value of over 85. BIS values between 60 and 80 were accepted for moderate sedation according to the adjusted BIS system (see table 1). Then the intravenous bolus injection of midazolam 0.03~0.3 mg/kg (En-Hua Pharmaceutical, Jiangsu province, China) was injected slowly first until the BIS value was between 60 and 80. In order to maintain the BIS value within the range of 60–80, the midazolam dose was regulated using a continuous infusion pump.

Outcome measurements

BISs value and Ramsay scores

According to the Ramsay scoring system, six different levels of sedation were defined (see box 1). Ramsay scores were determined before sedation and every hour after sedation for 6 h continuously. At the same time, BIS values were dynamically recorded. The signal quality index (SQI) bar measured the reliability of the signal. Higher SQI numbers indicated more reliable BIS values. When the SQI was more than 90%, the BIS value was considered valid and recorded (figure 2).

Other outcomes

Hourly dosages of midazolam after sedation were recorded continuously for 6 h, and hourly mean doses within the first 6 h were calculated. The relevant parameters of the acute physiology and chronic health evaluation II (APACHE II) and multiple organ dysfunction (MOD) score were calculated and recorded before sedation and the first 2 days after sedation. Simultaneously, the results of liver function and renal function were recorded. In addition, adverse reactions, including respiratory depression, hypotension, abdominal distension, nausea, vomiting, delayed bowel movement, rash, hallucinations, headache, thrombophlebitis and ataxia, were observed. The costs of midazolam within the first 6 h were calculated at the same time.
Table 1 Adjusted depth of sedation as measured by the BIS system

<table>
<thead>
<tr>
<th>BIS system value</th>
<th>Depth of sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Flat-line EEG</td>
</tr>
<tr>
<td>0–40</td>
<td>Deep hypnotic state; memory function lost; increasing burst suppression</td>
</tr>
<tr>
<td>40–60</td>
<td>Recommended range for general anaesthesia</td>
</tr>
<tr>
<td>60–80</td>
<td>Recommended range for sedation</td>
</tr>
<tr>
<td>85–100</td>
<td>Awake; memory intact</td>
</tr>
</tbody>
</table>

BIS, bispectral index.

Box 1 Ramsay sedation scale

<table>
<thead>
<tr>
<th>Level characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Patient awake, anxious, agitated or restless</td>
</tr>
<tr>
<td>2 Patient awake, cooperative, oriented, and tranquil</td>
</tr>
<tr>
<td>3 Patient drowsy, with response to commands</td>
</tr>
<tr>
<td>4 Patient asleep, brisk response to glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>5 Patient asleep, sluggish response to stimulus</td>
</tr>
<tr>
<td>6 Patient has no response to firm nail-bed pressure or other noxious stimuli</td>
</tr>
</tbody>
</table>

Statistics

Data were reported as mean plus or minus SD. The various outcomes among the control group (group A), the acupuncture-treated group (group B) and the electroacupuncture-treated group (group C) were compared using a one-way analysis of variance test, S–N–K test with SPSS 16.0 software. The relationship of the BIS value and the Ramsay score was analysed using rank correlation analysis. Values were considered significantly different when p<0.05.

RESULTS

Patient data

Among the enrolled patients, there were four cases of severe acute pancreatitis, six cases of acute myocardial infarction, four cases of acute heart failure, 18 cases of respiratory failure, four cases of mitral valve replacement surgery, one case of infective endocarditis, two cases of drowning, two cases of septic shock, three cases of rectal cancer after radical resection and one case of gastric cancer after radical resection. Twenty-six male and 19 female patients were included in the trial. With regard to age, sex, weight, APACHE II score, MOD score, there was no significant differences among the control group (group A), the acupuncture-treated group (group B) and the electroacupuncture-treated group (group C) were compared using a one-way analysis of variance test, S–N–K test with SPSS 16.0 software. The relationship of the BIS value and the Ramsay score was analysed using rank correlation analysis. Values were considered significantly different when p<0.05.

Dynamic changes in BIS values and Ramsay scores after sedation over 6 h

There was a strong, negative correlation between the BIS value and Ramsay score, which was statistically significant (r = 0.859, p < 0.01). However, at all time points of the sedation process, there were no significant differences in BIS values and Ramsay scores between groups A and B, groups A and C and groups B and C (tables 3 and 4).

Dynamic changes in hourly dosage of midazolam after sedation over 6 h

The hourly mean dosage of midazolam was 0.08 (±0.03 mg/kg per hour) in group A, 0.07 (±0.01 mg/kg per hour) in group B and 0.05 (±0.02 mg/kg per hour) in group C, respectively. There was no difference between groups A and B in the dosage of midazolam (p = 0.189). However, the hourly mean dosage of midazolam was significantly decreased in group C, compared with groups A and B (C vs A p = 0.001; C vs B p = 0.021). Among the three groups, the loading doses of midazolam at the start of sedation were similar. In the first hour of continuous sedation injected with an infusion pump, there was no significant difference in the dosage of midazolam in the three groups, and there was no significant difference in the dosages of midazolam between group A and group B from the second hour to the sixth hour. However, the dosages of midazolam in group C were significantly less than those in group A and group B after 2 h (figure 3).

Changes in liver function and renal function

Not only between-group comparison analysis on the dynamic changes in liver function and renal function (see supplementary tables S6 and S7, available online only), but also before and after comparison analysis showed no statistical differences (p>0.05 all).

Adverse effects

After the application of midazolam for sedation in 45 patients, there were four cases of hypotension, which could easily be reversed to normal levels after rehydration, including two cases in group A, one case in group B and one case in group C; three cases of abdominal distention, including two cases in group B, one case in group C; one case of vomiting also occurred in group A. No obvious rash, hallucination, headache, thrombophlebitis or ataxia occurred in any group. In addition, after the acupuncture needles were removed, there was no obvious bleeding at the acupuncture points.

DISCUSSION

In ICU, life support is performed for critically patients. As a result of serious illness in itself (such as pain, hypoxia, etc) or a relatively poor environment (such as open ICU ward, noise, invasive medical manipulation, etc), psychological problems often occur in many patients, for instance, delirium develops in 20–50% of lower severity ICU patients or those not receiving mechanical ventilation and in 60–80% of ICU patients receiving mechanical ventilation. In fact, sedation is given to ensure comfort and to minimise distress, but is linked to delirium and immobility. There has recently been a move in the USA and Europe to reduce sedation aggressively and mobilise intensive care patients. Even the outcomes of critically ill patients can be improved by applying evidence-based therapies for ‘liberation’ from mechanical ventilation and sedation, and ‘animation’
through early mobilisation. Therefore, proper analgesia and sedation are the important adjunct therapy for critically ill patients in ICU, especially those with mechanical ventilation.

However, there are still two confusing problems about sedative agents at present. First, clinicians have traditionally relied on subjective, imprecise and delayed measures of sedation for critical patients under mechanical ventilation. As the first scale to be defined for sedated patients, the Ramsay score was most commonly used clinically, but has disadvantages in the following five aspects: (1) Based on subjective judgement, the same patient, assessed by different clinical staffs, can be given very different Ramsay scores. (2) Ramsay scores, only being divided into six levels, lack sensitivity regarding the level of sedation. (3) The assessment of sedation often requires an assessment of the response to a stimulus, which may be noxious, such as pain or discomfort. (4) Among patients with mechanical ventilation, the depth of sedation cannot be evaluated in those who require a certain degree of muscle relaxation, especially in the application of inverse ratio ventilation or high positive end-expiratory pressure. (5) Assessment of sedation is time consuming and increases staff workload. However, BIS monitoring addresses these shortcomings to a large extent. In particular, the monitor can be used as part of an integrated approach for the evaluation of those patients especially when the subjective scales do not work well in the setting of neuromuscular blockade or may not be sufficiently sensitive to evaluate very deep sedation. As a kind of new mode for objective, real-time monitoring of sedation, BIS even avoids the implementation of external stimuli.

BIS is a quantitative analysis indicator of EEG including frequency, amplitude and phase characteristics, which can better preserve the original features of EEG information. Some studies have found a good correlation between BIS and the sedation–agitation scale, Ramsay score and COMFORT score in assessing the depth of sedation in patients treated with mechanical ventilation in ICU. BIS may best be used to identify and prevent over or under-sedation of mechanically ventilated patients in the ICU. Therefore, it is more valuable to evaluate the depth of sedation by the BIS value, especially in the ICU. However, some studies have found that BIS did not reliably predict sedation depth as measured by clinical evaluation in ICU patients, because of large interindividual variability, the discrepancy between left and right brain and discordance between high BIS values and deep clinical sedation, especially discrimination between very deep, deep to moderate, and no sedation after general anaesthesia. In our study, all patients received midazolam for 6 h. BIS values were maintained from 60 to 80, equivalent to Ramsay scores in two to three levels of sedation. An in-depth analysis of results revealed a good correlation between BIS values and Ramsay scores in our ICU. This suggests that the BIS monitor can offer several benefits: more objective by reducing human error, intuitive, continuous observation and relatively stable. However, BIS values should still be interpreted with caution, because electromyographic activity and other factors seem to confound BIS scores. Even the relation between BIS and the depth of sedation may not be independent of anaesthetic agents. The effect of electroacupuncture on BIS measurement thus needs to be given attention. Actually, in our study, we found that if electroacupuncture stimulation was given throughout the whole process of sedation, it was difficult to use BIS monitoring simultaneously. Therefore, in our experiment, BIS values were intermittently recorded only in the periods when electroacupuncture was not being used. Usually, BIS values were recorded before re-starting electroacupuncture stimulation, so that the readings were reliable without electrical interference.

Second, it is difficult to avoid the side effects of sedative drugs completely, for example, respiratory depression, hypotension, bradycardia, drug excess accumulation, drug resistance and liver and kidney dysfunction. Sedative drugs can even induce true physical dependence and psychological dependence, with or without addiction, leading to drug withdrawal difficulties, increasing the economic burden of long-term ICU patients. This could enhance the role of acupuncture in treatment for sedation and for analgesia. Numerous studies have demonstrated that the nervous system, neurotransmitters and endogenous substances may respond to needling stimulation and electrical acupuncture. Electroacupuncture can ease the pain by opioid peptides in the periaqueductal gray, which can be a possible mechanism for reducing the dose of midazolam. Research has demonstrated that activation of both the μ and κ receptors could produce an analgesic effect. Other substances, including serotonin, catecholamines, inorganic chemicals and amino acids such as glutamate and γ-aminobutyric acid, are proposed to mediate certain cardiovascular and analgesic effects of acupuncture. In our experiment, we selected acupuncture points used for calming the nerves according to traditional Chinese

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### Table 2 Comparison of baseline characteristics of the three groups ($\overline{x} \pm S$)

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender (M/F)</th>
<th>Age (years) $\overline{x} \pm S$</th>
<th>Weight (kg) $\overline{x} \pm S$</th>
<th>APACHE II Score $\overline{x} \pm S$</th>
<th>MOD score $\overline{x} \pm S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=15)</td>
<td>9/6</td>
<td>57.6 ± 13.0</td>
<td>60.2 ± 7.8</td>
<td>15.07 ± 3.63</td>
<td>7.47 ± 4.09</td>
</tr>
<tr>
<td>B (n=15)</td>
<td>10/5</td>
<td>55.8 ± 17.0</td>
<td>60.0 ± 8.2</td>
<td>13.80 ± 3.95</td>
<td>7.27 ± 3.63</td>
</tr>
<tr>
<td>C (n=15)</td>
<td>7/8</td>
<td>58.5 ± 18.8</td>
<td>59.6 ± 9.2</td>
<td>13.67 ± 3.50</td>
<td>8.93 ± 3.06</td>
</tr>
</tbody>
</table>

$n=15$ in each group. Values are means ± SD. No significant differences between groups.

APACHE II, acute physiology and chronic health evaluation II; MOD, multiple organ dysfunction.
medicine theory. Therefore, similar to a study on sedative effects during mechanical ventilation after valve replacement, Yintang and GV24 were selected as appropriate acupuncture points.39

To find a way forward to solve these two problems, BIS was used to evaluate the general sedative effect of a combination of electroacupuncture and midazolam. The results showed that, compared with groups A and B, the dosage of midazolam in group C was notably decreased after 2 h of continuous sedation injected with an infusion pump, suggesting an additive sedative effect in critically ill patients during mechanical ventilation. Sedation with electroacupuncture might reduce the costs of sedation, but we found no reduction in our short-term study. Furthermore, it should not be assumed that 6 h of treatment could improve the prognosis of electroacupuncture patients. These are suitable topics for further research.

The US Food and Drug Administration has approved information on midazolam injection for healthcare professionals and patients. It includes warnings on adverse reactions. Respiratory depression was ruled out by the use of mechanical ventilation. Often, side effects occur when starting, adjusting or terminating the administration of the drug. For example, hypotension occurred when a bolus of midazolam was given initially, and abdominal distension was observed during therapy but reduced when the treatment ended. In this study, adverse reactions to midazolam were similar in the three groups, although the dosages of midazolam in group C were far less than those in group A and group B. However, we cannot conclude from this exploratory study that electroacupuncture has no effect on the adverse reaction of midazolam, and further studies in larger samples are necessary.

In summary, the combination of electroacupuncture and midazolam can markedly reduce the dose of sedative drug (midazolam), without any apparent severe adverse reaction.

Table 3 Comparison of BIS value among three groups (mean and SD) (\(\bar{x} \pm S\))

<table>
<thead>
<tr>
<th>Group</th>
<th>Admitted into ICU</th>
<th>Start of sedation</th>
<th>The first 6 h after sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 h</td>
</tr>
<tr>
<td>A</td>
<td>15</td>
<td>71.60±17.11</td>
<td>87.33±3.37</td>
</tr>
<tr>
<td>B</td>
<td>15</td>
<td>65.93±19.66</td>
<td>91.20±4.30</td>
</tr>
<tr>
<td>C</td>
<td>15</td>
<td>70.53±20.74</td>
<td>88.20±3.69</td>
</tr>
</tbody>
</table>

n=15 in each group. Values are means±SD. No significant differences between groups at any time. BIS, bispectral index; ICU, intensive care unit.

Table 4 Comparison of Ramsay score among three groups (\(\bar{x} \pm S\))

<table>
<thead>
<tr>
<th>Group</th>
<th>Admitted into ICU</th>
<th>Start of sedation</th>
<th>The first 6 h after sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 h</td>
</tr>
<tr>
<td>A</td>
<td>15</td>
<td>3.13±1.64</td>
<td>1.40±0.51</td>
</tr>
<tr>
<td>B</td>
<td>15</td>
<td>3.00±1.69</td>
<td>1.27±0.46</td>
</tr>
<tr>
<td>C</td>
<td>15</td>
<td>2.93±1.58</td>
<td>1.40±0.51</td>
</tr>
</tbody>
</table>

n=15 in each group. Values are means±SD. No significant differences between groups at any time. ICU, intensive care unit.

Summary points
- Midazolam is used to sedate intubated patients
- We tested acupuncture as an adjunct
- EA, though not manual acupuncture, allowed reduction of the dose of midazolam

Figure 3 The comparison of the dosages of midazolam 6 h after sedation among three groups. The hourly mean dosage of midazolam was significantly decreased in group C, compared with groups A and B after 2 h # represents the comparison between groups C and A (control), \(\#\) \(p<0.05\) and \(\#\ #\) \(p<0.01\); \(\Delta\) represents the comparison between groups C and B (control), and \(\Delta\ p<0.05\) and \(\Delta\ \Delta\ p<0.01\) (n=15 in each group).
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Acupunct Med 2012 30: 78-84 originally published online March 29, 2012
doi: 10.1136/acupmed-2011-010095

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