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Original Article

The effects of spinal anesthesia on ED_{50} and BIS_{50} of etomidate for loss of consciousness: a randomized controlled, sequential allocation trial

Ningkang Li[1*], Fan Yang[2*], Yonghai Zhang[2], Liyan Zhao[1], Di Zhu[1], Qinghong Lei[2], Hanxiang Ma[2]

[1]Department of Anesthesiology, Ningxia Medical University, Yinchuan 750004, P. R. China; [2]Department of Anesthesiology, General Hospital of Ningxia Medical University, Yinchuan 750004, P. R. China. [*]Equal contributors.

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Abstract: Objectives: The purpose of this sequential study was to investigate the effects of spinal anesthesia on the median effective dosage (ED_{50}) of etomidate for loss of consciousness (LOC) and the BIS value of etomidate for LOC of 50% of patients (BIS_{50}). Methods: A total of 46 patients scheduled for elective gynecological operations were randomly allocated to two groups to receive either etomidate alone (group E, n = 26) or etomidate combined with spinal anesthesia (group ES, n = 20). Patients in the group ES received spinal anesthesia (3 ml of 0.5% hyperbaric bupivacaine) before the injection of etomidate for sedation. The first patient in group E received 0.089 mg·kg^{-1} of etomidate, and the first patient in group ES received 0.076 mg·kg^{-1} of etomidate 15 minutes after spinal anesthesia. The dosage of etomidate required for the next patient was determined by the up-and-down method in the two groups. The ED_{50} and BIS_{50} of etomidate for LOC were determined by the Bliss method and the isotonic regression method. The bootstrap approach was used to estimate the 83% confidence intervals (83% CIs) of ED_{50} and BIS_{50}. Results: The ED_{50} of etomidate for LOC was 0.103 mg·kg^{-1} (95% CI, 0.092 to 0.115 mg·kg^{-1}) in group E and 0.082 mg·kg^{-1} (95% CI, 0.075 to 0.090 mg·kg^{-1}) in group ES by the Bliss method, and the BIS_{50} was 59 (95% CI, 55 to 63) in group E and 69 (95% CI, 62 to 76) in group ES. From the isotonic regression method and the bootstrap approach, the ED_{50} was 0.105 mg·kg^{-1} (83% CIs, 0.100 to 0.110 mg·kg^{-1}) in group E and 0.083 mg·kg^{-1} (83% CIs, 0.080 to 0.087 mg·kg^{-1}) in group ES, and the BIS_{50} was 46 (83% CIs, 41 to 48) in group E and 56 (83% CIs, 51 to 62) in group ES. Conclusion: Patients with spinal anesthesia easily presented with LOC after the injection of etomidate, and spinal anesthesia affected the BIS value of etomidate for LOC.

Keywords: Etomidate, spinal anesthesia, ED_{50}, bispectral index, loss of consciousness

Introduction

The combination of spinal anesthesia with general anesthesia has many advantages, such as reducing circulatory and respiratory complications, shortening hospital length of stay [1] and potentially decreasing the tumor recurrence rate [2]. Bardia [3] reported that combined epidural-general anesthesia (EA-GA) improved the long-term survival rate compared with general anesthesia alone, and thus suggested that EA-GA should be strongly considered in appropriate patients. Over the past thirty years, many previous studies have demonstrated that neuraxial anesthesia (NA) (including epidural anesthesia and spinal anesthesia) significantly decreased the hypnotic dosage of midazolam [4], thiopental [4], propofol [5] and inhalation anesthetics [6, 7], indicating that NA has a direct sedative effect.

Unlike propofol (alkylphenol) and midazolam (benzodiazepine), etomidate is a carboxylated imidazole-derived hypnotic. It has a minimal effect on the cardiovascular system due to its lack of inhibition of myocardial function and sympathetic tone [8, 9]. As early 1983, research indicated that a continuous infusion of etomidate to supplement NA had a satisfactory result with a stable cardiovascular outcome and suggested that etomidate was a good choice for patients [9] whose blood pressure dropped after NA [10, 11]. Considering the sedative effect of NA, the dosage of etomidate

given to patients after NA should theoretically decrease, but this has not been demonstrated.

The bispectral index (BIS) has been demonstrated to be closely associated with the sedative level of drugs that act on the gamma-aminobutyric acid-A ($GABA_A$) receptor [12]. Thus, it has been commonly used to assess the depth of anesthesia and to maintain loss of consciousness (LOC) [13]. Previous studies had shown that the sedative effect induced by NA could also be well assessed by a BIS monitor [7, 14]. Many factors, including anesthetics, hypoglycemia, and cerebral ischemia affect the measurement of BIS values associated with a particular sedative level induced by a hypnotic [15]. However, the effect of spinal anesthesia on the BIS value of etomidate for LOC is unclear.

In this study, we aim to investigate the effect of spinal anesthesia on the median effective dosage (ED_{50}) of etomidate for LOC and the BIS value of etomidate for LOC of 50% of patients (BIS_{50}). The study tests the hypothesis that spinal anesthesia can significantly influence the ED_{50} and BIS_{50} of etomidate for LOC.

Methods

This study was approved by the Ethics Committee of the General Hospital of Ningxia Medical University (No.2017-151) and registered at ClinicalTrials.gov (NCT03240055). After obtaining written informed consent, we consecutively enrolled fifty-two female patients. The inclusion criteria were age 18-65 years with ASA physical status (ASA PS) I-II and a body mass index (BMI) between 18.0 and 24.5 $kg{\cdot}m^{-2}$ who were undergoing elective gynecological operations to which both general anesthesia or spinal anesthesia combined with sedation could be applied. The exclusion criteria were patients with hearing loss, psychiatric and central nervous system diseases, a history of drug and alcohol abuse, and an allergy or contraindication to bupivacaine and etomidate. The study was conducted at the General Hospital of Ningxia medical university, a tertiary hospital in Yinchuan, China. Patients were allocated following simple randomization procedures to one of two groups: group E to receive an etomidate injection alone (n = 26) and group ES to receive etomidate combined with spinal anesthesia (n = 20). Each random number with a pre-specified intervention (etomidate alone/etomidate combined with spinal anesthesia) was concealed by a series of sequentially numbered, opaque, and sealed envelopes. Each patient was assigned a sequentially numbered envelope by another attending anesthesiologist and received a pre-specified intervention.

No premedication was given before surgery. The operating room was kept warm to prevent an increase in EMG activity due to shivering. Ringer's lactate 500 ml was infused initially for pre-hydration, followed by a colloid or crystalloid solution infused at the rate of 10 $ml{\cdot}kg^{-1}{\cdot}h^{-1}$. Routine monitoring of the electrocardiogram (ECG), the mean arterial pressure (MAP), the pulse oximetry saturation (SpO_2), and the heart rate (HR) were performed. The bispectral quatro sensor was placed in the forehead as recommended by the instructions (Covidien, Mansfield, MA, USA). Before the initiation of anesthesia, the MAP, HR, SpO_2 and BIS were recorded as baseline. Patients in group ES received spinal anesthesia before the injection of etomidate for sedation. With patients in the right lateral decubitus position, the spinal puncture was performed with a 25 gauge pencil spinal needle (Jierui, Shandong, China) at the L_{3-4} interspace. 3 ml of 0.5% hyperbaric bupivacaine (Chaohui, Shanghai, China) was injected into the subarachnoid space at a rate of 0.2 mL/s. Cerebrospinal fluid aspiration (0.1 ml) was done to confirm correct needle placement before and after the hyperbaric bupivacaine injection. Then the patients were turned immediately to the supine position. The sensory block level was evaluated bilaterally using a pinprick test every 1 min until 15 min after spinal anesthesia, and bed tilting (upwards, horizontal, or downwards) was performed until a bilateral sensory block level was confirmed to remain at T_4-T_6. When the block level did not reach T_6 within 15 min after spinal anesthesia or when severe complications occurred after spinal anesthesia, the case was excluded from data collection. All anesthesia procedures and drug administration were conducted by a board-certified anesthesiologist who was aware of the allocation of each patient. The first patient in group E received intravenously (IV) 0.089 $mg{\cdot}kg^{-1}$ of etomidate (Nhwa Pharmaceutical, Jiangsu, China), and the first patient in group ES received an IV with 0.076 $mg{\cdot}kg^{-1}$ of etomidate at 15 min after spinal anesthesia.

Table 1. Responsiveness scores of the Modified Observer's Assessment of Alertness/Sedation Scale

Score	Response
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking
0	Does not respond to noxious stimulus

The dosage of etomidate for the next patient from each group was decreased or increased by 15% of the dosage administered to the previous patient, depending on the unconsciousness or consciousness level of the previous patient. The various dosages of etomidate were given to each patient for 20 seconds. The sample size was based on the up-and-down method, in which the testing of different dosages of etomidate continued in consecutive patients until a sample size of seven crossover points from "consciousness" to "unconsciousness" was reached in each group [16]. Patients were excluded from data collection if hypoxemia (SpO_2 < 95%) appeared after the administration of etomidate, and they were treated by manually-assisted ventilation. The primary outcomes were ED_{50} and BIS_{50} of etomidate for LOC. The conscious state of each patient after the injection of etomidate was assessed at 4-5 second intervals for 3 minutes by one observational investigator who was blinded to the grouping. The minimum BIS values of each patient were recorded during this process. Patients were considered to be conscious if the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) (**Table 1**) was ≥ 3 and considered to be unconscious if the MOAA/S ≤ 2. The secondary outcomes were MAP and HR. The MAP and HR were recorded at l min (T_1), 2 min (T_2), 3 min (T_3), and 5 min (T_4) after they were administered an etomidate IV. Bradycardia was defined as HR < 45 beats/min and was treated by atropine 0.5 mg. Hypotension was defined as MAP < 65 mmHg or < 30% of the baseline and was treated by ephedrine 4-6 mg.

Statistical analysis was performed using the SPSS ver. 17.0 for Windows (SPSS Inc., IL, USA) and R for Windows (R ver. 3.2.2). Data were expressed as the mean ± SD or the number of cases as appropriate. Continuous data (age, height, weight, saturation, BIS value) were analyzed between the two groups by the independent Student's *t* test or the Mann-Whitney U test. The categorical data (ASA PS) were analyzed between two groups using an χ^2 test. A two-sided *P* value of less than 0.05 was considered statistically significant. The ED_{50}, BIS_{50} and 95% confidence interval (CI) were calculated by the Bliss method, which is the most effective one among the methods for calculating the median effective dosage. Firstly, this method collects the number of sequential cases of positive (unconsciousness)/negative (consciousness) reactions by the sequential allocation trial, and then the effective number (positive number) and invalid number (negative number) of each dosage group are counted. In addition, the logarithm, positive rate and the total number of patients of each dosage group are also calculated. The above data are substituted in the median effective dosage formula to calculate the ED_{50} and 95% CI. BIS_{50} is also calculated according to this method. For backup and sensitivity analysis, an isotonic regression method based on the pooled adjacent-violators algorithm (PAVA) was used to estimate the ED_{50} and BIS_{50}, and the 83% CIs was estimated using a bootstrap approach. The isotonic regression is a nonparametric statistical method, and the samples do not require normal distribution. The above statistical steps are implemented by R for Windows. The method of overlapping CIs (83% CIs) was used to compare ED_{50} and BIS_{50} between the two groups. If 83% CIs were non-overlapping, the null hypothesis of equal ED_{50} and BIS_{50} was rejected at α of approximately 0.05 [17].

Results

The CONSORT flow diagram of the study is shown in **Figure 1**. The study was conducted from June 2017 to July 2017. The primary analysis was per-protocol analysis for the requirement of the up-and-down method. We assessed fifty-two patients for their eligibility to participate in this study. Two patients did not meet the inclusion criteria, two declined to participate, and then we randomized the remaining forty-eight patients. Twenty-seven patients were allocated to group E and twenty-one to group ES. One patient needed oxygen mask inhalation to maintain SpO_2 > 95% after being administered an etomidate IV in group E, which would inter-

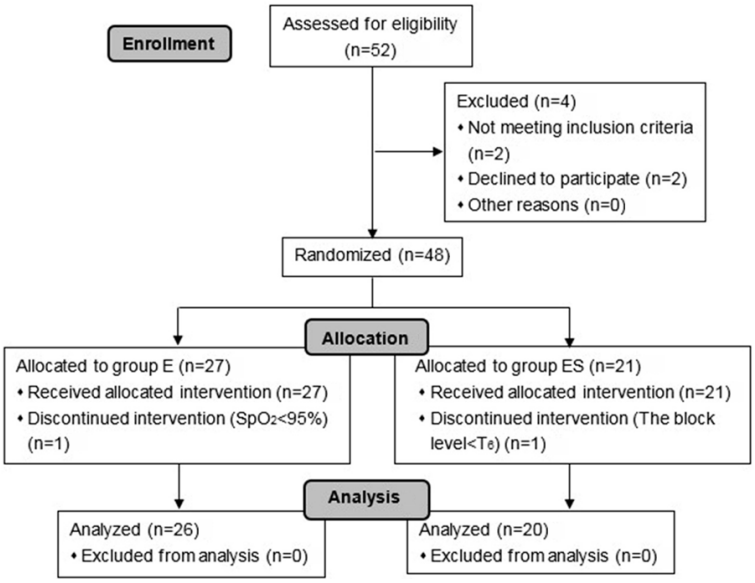

Figure 1. CONSORT flow diagram. E, etomidate; ES, etomidate combined with spinal anesthesia.

Table 2. Patient characteristics, saturation and BIS value data

Variable	E (n = 26)	ES (n = 20)
Age (years)	41 ± 9	42 ± 11
Height (cm)	160 ± 4	161 ± 3
Weight (kg)	55 ± 5	56 ± 5
ASA PS (I/II)	17/9	11/9
Saturation (%)*	98 ± 2	97 ± 2
BIS value*	95 ± 3	96 ± 1

The data are represented by mean ± SD or absolute numbers. ASA PS, American Society of Anesthesiologists physical status. BIS, Bispectral Index. *Values obtained at baseline. E, etomidate; ES, etomidate combined with spinal anesthesia.

fere with the patient's conscious state assessment, so this patient was excluded from further analysis. One patient in group ES was excluded from further analysis because her block level < T_6 after spinal anesthesia. Therefore, forty-six patients were included in the analysis. There were no significant differences between the two groups in patient characteristics, saturation and BIS measurements at baseline (**Table 2**).

The up-and-down results in consecutive patients are shown in **Figure 2**. The ED_{50} of etomidate were 0.082 mg·kg^{-1} (95% CI, 0.075 to 0.090 mg·kg^{-1}) and 0.103 mg·kg^{-1} (95% CI, 0.092 to 0.115 mg·kg^{-1}) in the ES group and E group by the Bliss method, respectively. The BIS_{50} for the LOC were 69 (95% CI, 62 to 76) and 59 (95% CI, 55 to 63) in the ES group and E group by the Bliss method, respectively. From the isotonic regression and bootstrap approach, the ED_{50} were 0.083 mg·kg^{-1} (83% CIs, 0.080 to 0.087 mg·kg^{-1}) and 0.105 mg·kg^{-1} (83% CIs, 0.100 to 0.110 mg·kg^{-1}) in the ES group and E group, respectively. The BIS_{50} values were 56 (83% CIs, 51 to 62) and 46 (83% CIs, 41 to 48) in the ES group and E group by the isotonic regression and bootstrap approach, respectively. Using the 83% CIs from the bootstrap distribution, the differences of ED_{50} and BIS_{50} between the ES and E groups were statistically significant ($P < 0.05$).

The MAP and HR values are illustrated in **Figure 3**. At baseline, the MAP and HR values between the two groups were not statistically different (both $P > 0.05$). The MAP at T_1, T_2, T_3, T_4 and the HR at T_1, T_3 after the administration of etomidate were significantly decreased in the ES group compared to the E group (all $P < 0.05$). One patient developed hypotension in group ES and recovered by the injection of ephedrine.

Discussion

Our study demonstrated that spinal anesthesia with bupivacaine decreased the ED_{50} and affected the BIS_{50} of etomidate for LOC. Namely, patients with spinal anesthesia were more sensitive to etomidate.

In the present study, we found that bupivacaine spinal anesthesia with the block level at T_4-T_6 decreased the ED_{50} of etomidate for LOC by 20%. This is inconsistent with some previous studies, which had demonstrated that the block level at T_7-T_9 after spinal anesthesia lead to a 36%-80% decrease in the dosages of thiopental, midazolam, and propofol when patients were sedated [4, 18-20]. Hodgson and colleagues [6] found that a thoracic epidural block could decrease the dosage of sevoflurane by 34% when the BIS values were kept at 50. The

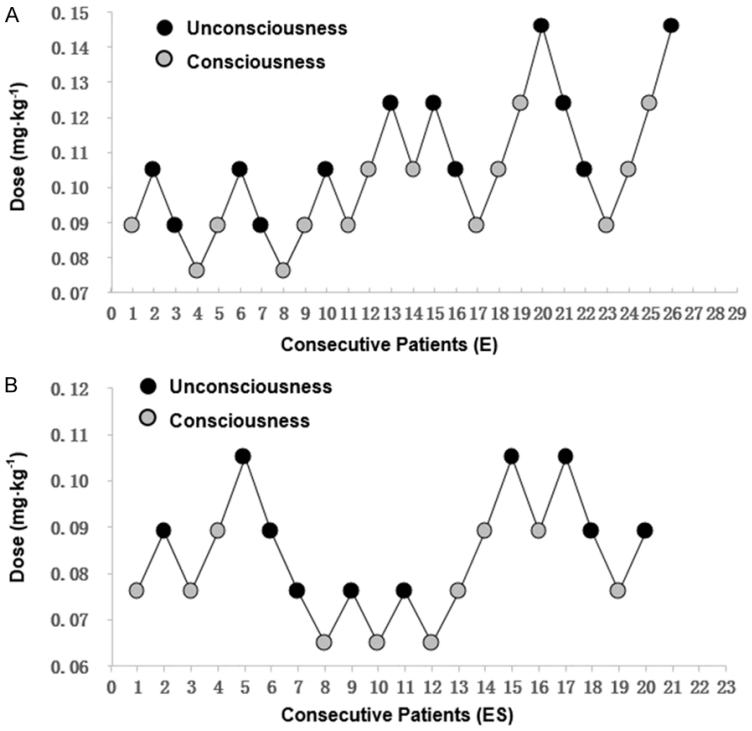

Figure 2. Up-and-down sequential allocation study of etomidate for LOC in the study groups. A. The calculated median effective dosages (ED_{50}) were 0.103 mg·kg^{-1} for group E. B. The calculated ED_{50} was 0.082 mg·kg^{-1} for group ES. E, etomidate; ES, etomidate combined with spinal anesthesia.

previous studies showed that 15min was not long enough for spinal anesthesia to achieve appropriate sedation effects [5, 21]. Also, the study by Kurup [22] and Pollock [23] showed that the sedative effects were most pronounced at 34 and 60 minutes after spinal anesthesia, respectively. This might explain why there was an only 20% decrease in the ED_{50} of etomidate for LOC by the spinal anesthesia in our study, at which the maximum sedative effect did not exert at 15 min after spinal anesthesia. Furthermore, the sedatives studied in previous studies were different from the agent in our study.

In the up-and-down sequential technique, the ideal dosages given to the first patient in each group were as close as possible to the actual ED_{50} of any study drugs. Considering that the ED_{50} of etomidate for LOC was 0.105 mg·kg^{-1} as determined by a previous study [24], the initial dosage given was 0.089 mg·kg^{-1} in group E because the subjects were female, and 0.076 mg·kg^{-1} in group ES for the sedative effect of spinal anesthesia.

The sedative effects of spinal anesthesia have been demonstrated over the past 30 years, and it was obvious in the high blockade level [5]. Up to the present, the speculated mechanism of the sedative effect of spinal anesthesia is considered to be the deafferentation theory [5]. Namely, spinal anesthesia can decrease the transmission of facilitatory sensory signals to the reticular activating system, which plays a critical role in regulating wakefulness. In addition, there are some other possible mechanisms that can explain the sedative effect of spinal anesthesia, including the systemic general anesthetic effect of absorbed local anesthetics [20, 23] and rostral spreading through the cerebrospinal fluid with a direct effect on the brain [23, 25].

BIS correlated well with the sedation level of propofol [26]. Meanwhile, Kaneda [27] showed that BIS was a reliable monitor for evaluating the depth of anesthesia during etomidate sedation. The mechanisms of etomidate and propofol exerted a sedative effect by the enhancement of the receptor's affinity for $GABA_A$ and may explain why a BIS monitor can be used to detect the depth of anesthesia. In our study, we found that the BIS_{50} of etomidate for the LOC was influenced by spinal anesthesia, and, namely, the extent to which the BIS values decreased was less when the patients were sedated by etomidate combined with spinal anesthesia than when the BIS values were decreased by sedation by etomidate alone. The observation was consistent with the findings of an earlier study, in which the BIS values were significantly lower with general anesthesia alone compared with combined epidural-general anesthesia [28]. One possible explanation for this might be that the BIS value only correlated well with the dosage/concentration of some hypnotics [26] but did not correlate well with spinal anesthesia. In our study, the sedative dosage of etomidate was reduced significantly when combined with

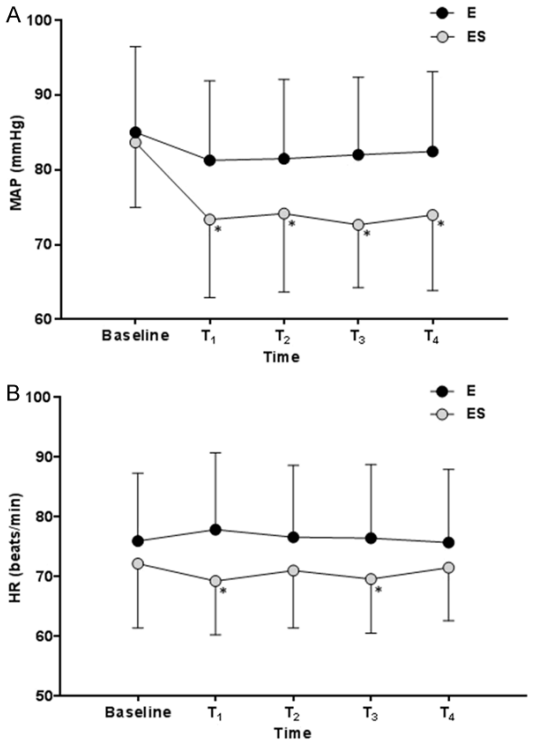

Figure 3. Hemodynamic profiles during the process of the experiment. A. The change of MAP. B. The change of HR. *MAP* mean arterial pressure; *HR* heart rate. *Baseline* before the initiation of anesthesia. T_1, T_2, T_3, and T_4 1, 2, 3, and 5 min after administered etomidate IV. E, etomidate; ES, etomidate combined with spinal anesthesia. *P < 0.05 statistically significant difference between the groups.

spinal anesthesia, and the BIS value was consequently higher. Another possible explanation might be that the BIS was not a sensitive enough indicator to detect the sedative effect within 15 min after the spinal anesthesia. Iida [21] showed that the BIS value was not significantly decreased within 15 min after spinal anesthesia. Pollock and colleagues [23] reported that the BIS value decreased only at 60 min after spinal anesthesia. Thus, it is possible that BIS could not detect the sedative effect of the spinal anesthesia in our study as the time point chose to evaluate the BIS value was 15 min after spinal anesthesia. In addition, BIS was used to detect the cortical EEG activity [5, 12], but the action site of the spinal anesthesia was the spinal cord.

Previous study showed that spinal anesthesia had a sedative effect, which could be measured by a new device - the Patient State Analyzer (PSA-4000), a monitor that was more sensitive to a slight change in the level of consciousness [22]. The BIS monitor is a relatively mature technique to evaluate the sedation depth in clinical practice. However, the PSA-400 monitor was not a commonly used device, so the BIS monitor was selected to measure the depth of anesthesia in our study.

Procedural sedation or general anesthesia induction of patients after NA by hypnotics are frequently performed in clinical practice. However, the combined anesthesia technique usually causes hypotension [7], especially when propofol is used [29]. In the present study, the patients had been sedated by etomidate, and we found that although there was a statistically significant decrease in MAP in the ES group compared to the MAP in the E group, this change had no clinical significance. Moreover, as to the surgical and experimental requirements, the sensory block level remained at T_4-T_6 in our study, which had a greater impact on hemodynamics, but only one patient with hypotension was observed among the etomidate-sedative patients.

All of the patients in our study were female, but Meibohm and colleagues [30] reported that the gender difference did not have a substantial effect on pharmacokinetics of a single-dosage. In addition, noise was unavoidable in the operating room [21], which might influence the precise measurement of the BIS value, which should be measured by a more precise device. But the effect of this confounding factor could be eliminated theoretically by the randomizing procedure in our study. Thirdly, the patients allocated to the intervention group were aware of the allocation, but it could not influence the outcome of the objective measurement we used.

In conclusion, we have investigated the effects of spinal anesthesia on the ED_{50} and BIS_{50} of etomidate for LOC in gynecological patients. The results demonstrated that spinal anesthesia can reduce the requirement of etomidate for LOC by 20% and affect the BIS value without hemodynamic instability.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hanxiang Ma, Department of Anesthesiology, General Hospital of Ningxia Medical University, 804 Shengli Street, Yinchuan 750004, Ningxia, P. R. China. Tel: +86-13519591508; Fax: +86-951-4082981; E-mail: mahanxiang@hotmail.com

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