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# Propofol decreased the etomidate-induced myoclonus in adult patients: a meta-analysis and systematic review

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**Abstract. – OBJECTIVE:** **Myoclonus is one of the main complications of etomidate anesthesia, which would develop into serious consequences during surgery. The present analysis was performed to evaluate systematically the effect of propofol on preventing etomidate-induced myoclonus in adult patients.**

**MATERIALS AND METHODS:** **Systematic electronic literature search was performed in the databases PubMed, Cochrane Library, OVID, Wanfang and China National Knowledge Infrastructure (CNKI) from inception to May 20, 2021, without any language restrictions. All randomized controlled trials evaluating the efficacy of propofol on preventing etomidate-induced myoclonus were enrolled. The primary outcome included the incidence and degree of etomidate-induced myoclonus.**

**RESULTS:** **1,420 patients (with 602 received etomidate anesthesia and 818 received propofol plus etomidate anesthesia) from 13 studies were eventually included. Whatever the intravenous propofol dose for anesthesia induction 0.8-2 mg/kg (RR:4.04, 95% CI [2.42,6.74] $p$<0.0001, $I^2$=56.5%), or the dose of propofol for anesthesia induction 0.5-0.8 mg/kg (RR:3.26, 95% CI [2.03,5.22] $p$<0.0001, $I^2$=0%), or the dose of propofol for anesthesia induction 0.25-0.5mg/kg (RR:1.68, 95% CI [1.1,2.56] $p$=0.0160, $I^2$=0%), combination of propofol and etomidate could significantly decrease the occurrence of etomidate-related myoclonus (RR=2.99, 95% CI [2.40, 3.71] $p$<0.0001, $I^2$=43.4%), compared with etomidate alone. In addition, propofol plus etomidate attenuated the incidence of mild (RR:3.40, 95% CI [1.7,6.82] $p$=0.0010, $I^2$=54.3%), moderate (RR:5.4, 95% CI [3.01, 9.67] $p$<0.0001, $I^2$=12.6%), severe (RR:4.15, 95% CI [2.11, 8.13] $p$<0.0001, $I^2$=0%) of etomidate-induced myoclonus without adverse effects except for the increased incidence of pain on injection (RR:0.47, 95% CI [0.26, 0.83] $p$=0.0100, $I^2$=41.5%) compared with etomidate alone.**

**CONCLUSIONS:** **The meta-analysis currently generates the evidence of combination of propofol with the dosage of 0.25-2 mg/kg and etomidate can alleviate the occurrence and severity of etomidate-induced myoclonus, with decreased incidence of postoperative nausea and vomiting (PONV) and comparative side effects of hemodynamic and respiratory depression of patients in comparison with etomidate alone.**

*Key Words:*
Etomidate, Myoclonus, Propofol, Meta-analysis.

### Abbreviations

GABA: Gamma-aminobutyric acid; NMDA: N-methyl-D-aspartate; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; CNKI: China National Knowledge Infrastructure; RCT: Randomized controlled trials GRADE: Grading of recommendations assessment, development, and evaluation system; RR: Risk ratio; CI: Confidence interval; MAP: Mean arterial pressure; HR: Heart rate; PONV: Postoperative nausea and vomiting; GLT1; Glutamate transporter 1. CA1: Cornus Ammonis 1.

## Introduction

Etomidate is widely used in clinical anesthesia as a sedative-hypnotic agent. Several attractive characteristics, such as stable hemodynamics and limited respiratory depression, make etomidate a more competitive alternative compared with



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other intravenous anesthetics especially in patients with cardiovascular disease[1]. Nevertheless, intravenous administration of etomidate usually is associated with myoclonus, with a reported incidence of 50-80%[2]. Some studies[3-5] reported several reasons on etomidate-induced myoclonus. Such as spontaneous nerve transmissions when the skeletal muscle control becomes more sensitive with the interruption of gama-aminobutyric acid (GABA) neurons[3], seizure-like activity[4] and depression of inhibitory neuronal circuits prior to excitatory neuronal circuits[5]. However, the exact mechanism of etomidate-induced myoclonus remains uncertain.

Propofol has been recognized as a classical sedative agent; characteristics such as fast onset time of action, short half-time, and rapid achievement of sedative depth make it becomes extremely widely used[6]. Several studies[7] reported that propofol can promote subcortical seizure activity and its effect on seizure duration is dose-dependent[8]. However, the combination of propofol and etomidate has been proved[9] that it improves hemodynamic stability, minimal respiratory depression, and can significantly decrease the risk of myoclonus compared to etomidate alone. Which may be due to the fact that propofol increases the strength of GABA-ergic neurotransmission and reversibly inhibits excitation at N-methyl-D-aspartate (NMDA) receptors[10]. Whether propofol can inhibit the etomidate-induced myoclonus remains controversial. There is a lack of high-quality meta-analysis concerning the combined use of propofol with different doses and etomidate for preventing the etomidate-induced myoclonus. Therefore, with the present meta-analysis and systematic review, we sought to integrate all the data assessing the efficacy of propofol with different doses on prevention of etomidate-induced myoclonus.

## Materials and Methods

### Data Sources and Search Strategy

Our systematic review was registered with PROSPERO, the international prospective register of systematic reviews of the National Institute for Health Research (www.crd.york.ac.uk/PROSPERO/#index. php, registration number CRD42021247281). The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[11] were followed. We performed a systematic electronic literature search in the databases PubMed, Cochrane Library, OVID, Wanfang and China National Knowledge Infrastructure (CNKI) from inception to March 20, 2022 without language restrictions. The search subject terms included myoclonus, propofol and etomidate, and the following search strategy was conducted in PubMed: ([myoclonus] OR [muscle spasm] OR [myoclonic movements] OR [seizure] OR [epilepsy] OR [convulsion]) AND [propofol] AND [etomidate] AND [randomized controlled trials].

### Inclusion and Exclusion Criteria

For inclusion, randomized controlled trials (RCTs) have the following characteristics:

Patients: Patients either sex scheduled for elective surgeries or examinations under general anesthesia.

Intervention: Studies with patients who have received propofol plus etomidate as an induction of anesthesia for surgery or endoscopy.

Comparison: Studies with patients who have received etomidate alone as an induction of anesthesia.

Outcomes: The primary outcome was the incidence of myoclonus and the severity of etomidate-induced myoclonus. Secondary outcome was recovery time, hemodynamic parameters and the incidence of adverse effects.

Exclusion criteria: RCTs that did not have the available outcome; studies with no full text; duplicate published articles, reviews, or lectures; pediatric patients.

### Assessment of Risks of Bias

We used the Cochrane Risk of Bias tool[12] to analyze the methodological quality of the studies by Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014); this analysis was done by two authors independently (Y.F., X.B.C.). This tool allowed for an assessment of the risks of selection bias (random sequence generation, allocation concealment), performance bias (blinding of participant and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data) and other bias (including the authenticity of clinical trials and whether the data are authentic and reliable, and the baseline characteristics are the same between the intervention groups and the comparison groups). When it was unclear if a domain was satisfactory, we contacted the first author of the trial to clarify the methodology. There are three categories included: low risk of bias, unclear risk of bias, or high risk of bias. We considered the trial to be at low risk of

bias when there was adequate random sequence generation, adequate allocation concealment and outcome assessment were adequately blinded. Trials were considered to be unclear risk of bias when the method of allocation concealment and blinding procedure were not mentioned. Trials were considered to be high risk of bias when sequence generated by some rule based on hospital or record number, an open random allocation schedule was used, no blinding or incomplete blinding was conducted.

### Data Extraction

Two reviewers (Y.F., X.B.C.) selected eligible studies independently, extracted data and recorded the trial characteristics with a standard data collection form. Any conflicts were resolved by mutual agreement. Data extracted included primary author, year of publication, sample size, comparative groups, outcome measures (occurrence rate of myoclonus, and severity of myoclonus), country, anesthetic techniques.

### Quality of Evidence

Grading of recommendations assessment, development, and evaluation system (GRADE)[13] was used to rate the quality of evidence and strength of our primary outcome and was judged by the following criteria: risk of bias, inconsistency, indirectness, imprecision, publication bias. The GRADE system assesses the quality of evidence in one of the following four levels: high certainty, moderate certainty, low certainty and very low certainty. When one of the above items was assessed as a risk, the evidence was downgraded by two levels or one level.

### Statistical Analysis

We used Stata/SE 12.1 (Statacorp LP 4905 Lakeway Drive College Station, TX, USA) for meta-analysis. The incidence and degrees of etomidate-induced myoclonus were reported by risk ratio (RR) and 95% confidence interval (CI). The $I^2$ coefficient was used to evaluate heterogeneity with predetermined thresholds for low (25-49%), moderate (50-74%), and high (>75%) levels. A random-effect model was applied in the event of moderate or high heterogeneity; otherwise, a fixed-effect model was used[14]. Subgroup analysis and sensitivity analysis were performed to identify potential methodological biases and subpopulations in which outcomes differed. Publication bias was assessed by using Begg's test and Egger's test when at least ten studies were included for the outcomes. A $p$-value lower than 0.05 was taken to indicate statistical significance.

## Results

### Study Selection

We identified 838 potentially relevant studies in the original search, 13 of these studies were eventually included in the meta-analysis based on the inclusion and exclusion criteria[15-27]. Figure 1 shows the flow chart of our study selection. The essential characteristics of all the included studies are shown in Table I.

### Risk of Bias Within Studies

Only one study[21] used an accurate method of random sequence generation and allocation concealment with the method of computer-generated random numbers table according to the items of Cochrane Risk of Bias tool[12]. All drugs were prepared by an anesthesiologist who was blinded to the study. An investigator, who was blinded to group assignment, assessed, and recorded all observed parameters in this study. The other twelve studies[15-20,22-27] did not mention the method of allocation concealment and blinding procedure. The methodological quality of thirteen studies[15-27] were given in Figure 2.

### Incidence of Etomidate-Induced Myoclonus

Among the thirteen RCTs, involving a total of 1,420 patients (with 602 received etomidate anesthesia and 818 received propofol plus etomidate anesthesia) described the incidence of etomidate-induced myoclonus. The incidence of etomidate-induced myoclonus in the propofol plus etomidate group and etomidate group was 12.7% and 46.2%, respectively. Low heterogeneity was found among the studies ($I^2$ =43.4%), a fixed-effect model was applied to conduct the meta-analysis. The result (Figure 3A) showed that combination of propofol and etomidate decreased the occurrence of etomidate-induced myoclonus (RR=2.99, 95% CI [2.40, 3.71], $p$<0.0001), compared with etomidate alone. A subgroup analysis was performed for the different doses of propofol (high dose: 0.8-2 mg/kg; moderate dose: 0.5-0.8 mg/kg; low dose: 0.25-0.5 mg/kg). The result showed that whatever the high dose of propofol for anesthesia induction 0.8-2mg/kg (RR:4.04, 95% CI [2.42, 6.74], $p$<0.0001, $I^2$=56.5%) (Figure 3B), or the moderate dose of propofol for anes-

thesia induction 0.5-0.8 mg/kg (RR:3.85, 95% CI [2.40, 6.18], $p<0.0001$, $I^2=0\%$) (Figure 3C), or the low dose of propofol for induction 0.25-0.5 mg/kg (RR:1.68, 95% CI [1.1, 2.56], $p=0.0160$, $I^2=0\%$) (Figure 3D). Co-administration of propofol and etomidate could significantly decrease the incidence of etomidate-induced myoclonus, compared with etomidate alone.

## Degree of Etomidate-Induced Myoclonus

### Mild myoclonus

Nine studies[15-18,20,22,24,26,27] reported the mild degree of etomidate-induced myoclonus, among the nine studies, one study[18] reported the incidence of mild myoclonus and there were not accurate data for respective incidence of moderate and severe myoclonus. The incidence of mild myoclonus was 27 out of 463 (5.8%) in the propofol plus etomidate group and 116 out of 462 (25.1%) in the etomidate group, respectively. A random-effect model was used with moderate heterogeneity ($I^2=54.3\%$), combination of propofol and etomidate decreased the incidence of etomidate-induced mild myoclonus, compared with etomidate alone in Figure 4A (RR: 3.40, 95% CI [1.7, 6.82], $p=0.0010$).

### Sensitivity analysis

One[24] of eight studies[15-17,20,22,24,26,27] included may have induced the heterogeneity without any

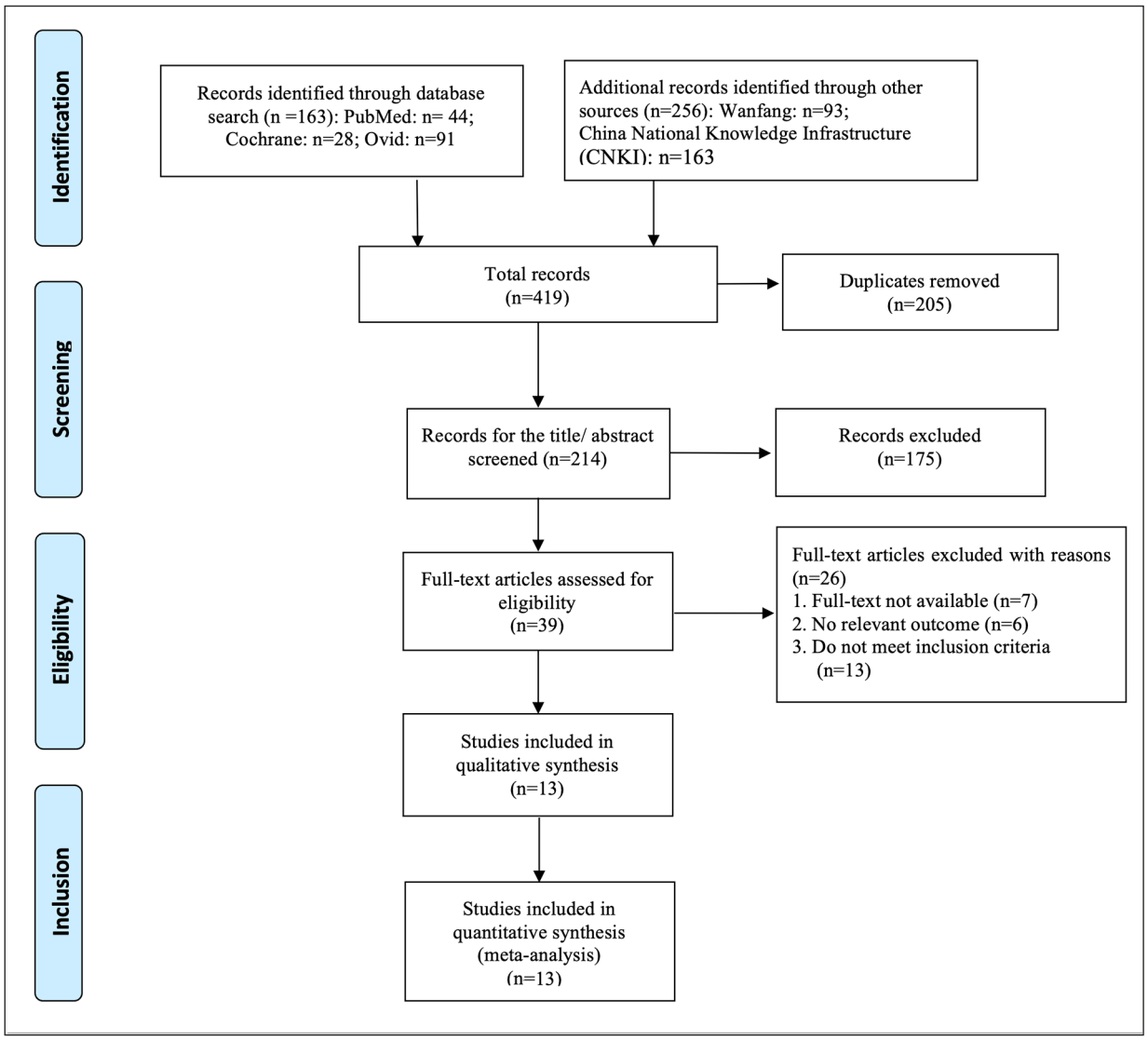


**Figure 1.** PRISMA flow diagram showing literature search results. Eligibility of studies for inclusion in meta-analysis.

| Study | Year | Number of patients | Dose of propofol | Dose of etomidate | Primary outcome: Incidence of myoclonus | | | | Other anesthesia techniques | Secondary outcome | Country | Surgery |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Total | Mild | Moderate | Severe | | | | |
| Jin et al[15] | 2012 | 30 | 0.6 mg/kg | 0.13-0.3 mg/kg | 0 | 0 | 0 | 0 | Propofol 5.5 mg/(kg·h) intravenously | Time of Calling for eye-opening, recovery time of odirectional force MAP, HR, RR, $SPO_2$ | China | Painless gastrointestinal endoscopy |
| | | 30 | 0 mg/kg | 0.13-0.3 mg/kg | 21 | 11 | 7 | 3 | | | | |
| Hu et al[16] | 2014 | 100 | 1 mg/kg | 0.2-0.3 mg/kg | 6 | 5 | 1 | 0 | Sufentanil 0.1 ug/kg intravenously | MAP, HR, RR, $SPO_2$; time of calling for eye-opening, recovery time of odirectional force adverse events: dizziness, vomiting and nausea, sleepiness, apnea | China | Induced abortion operations |
| | | 100 | 0 mg/kg | 0.2-0.3 mg/kg | 37 | 21 | 12 | 5 | | | | |
| Li et al[17] | 2014 | 30 | 0.6 mg/kg | 0.3 mg/kg | 2 | 2 | 0 | 0 | Midazolam 0.05 mg/kg, cisatracuramide 0.3 mg/kg, fentanil 2ug/kg | BP, DBP, HR | China | Laparoscopic cholecystectomy |
| | | 30 | 1.2 mg/kg | 0.3 mg/kg | 2 | 2 | 0 | 0 | | | | |
| | | 30 | 0 mg/kg | 0.3 mg/kg | 13 | 7 | 5 | 1 | | | | |
| Fu et al[18] | 2014 | 70 | 0 mg/kg | 0.3 mg/kg | 14 | 11 | | | | SBP, DBP, HR, $SpO_2$, eye-opening, recovery time | China | Painless colonoscopy |
| | | 70 | 0.8-1 mg/kg | 0.15 mg/kg | 2 | 2 | | | | | | |
| Zhao et al[19] | 2015 | 40 | 0.5-1 mg/kg | 0.2-0.25 mg/kg | 3 | | | | Fentanyl 0.1 mg intravenously | SBP, DBP, HR, $PO_2$, recovery time | China | Painless gastrointestinal endoscopy |
| | | 40 | 0 mg/kg | 0.2-0.25 mg/kg | 12 | | | | | | | |
| Lin et al[20] | 2015 | 50 | 1 mg/kg | 0.2 mg/kg | 12 | 8 | 4 | 0 | Rocuronium bromide 0.6 mg/kg intravenously | SBP, DBP, MAP, HR | China | Abdominal operation |
| | | 50 | 0 mg/kg | 0.4 mg/kg | 32 | 9 | 17 | 6 | | | | |
| Meng et al[21] | 2016 | 50 | 0 mg/kg | 0.15-0.2 mg/kg | 15 | | | | Intravenous (i.v.) 1 μg/kg fentanyl at 5-10 sec prior to gastroscopy | Recovery time, Side effects, including PONV, body movement, apnea (interval time of respiration, >30 sec), hypoxemia | China | Scheduled for gastroscopy under anesthesia |
| | | 50 | 1 mg/kg | 0.1 mg/kg | 2 | | | | | | | |
| Liu et a[22] | 2017 | 72 | 0 mg/kg | 0.2 mg/kg | 35 | 17 | 14 | 4 | | Circulation: MAP and HR; Respiration: the incidence of hypoxemia: adverse events: dizziness, vomiting, nausea, psychiatric symptoms | China | Painless gastrointestinal endoscopy |
| | | 71 | 0.25 mg/kg | 0.2 mg/kg | 19 | 6 | 10 | 3 | | | | |
| | | 73 | 0.5 mg/kg | 0.2 mg/kg | 12 | 6 | 5 | 1 | | | | |
| | | 74 | 0.75 mg/kg | 0.2 mg/kg | 11 | 8 | 2 | 1 | | | | |
| Wu et al[23] | 2017 | 20 | 0 mg/kg | 0.3 mg/kg | 7 | | | | Fentanyl 0.5ug/kg and 2% lidocaine hydrochloride 1 mg/kg intravenously | MAP, HR, $SPO_2$, recovery time, adverse events: hypotension, hypoxemia | China | Subpyloricendoscopic ultrasonography |
| | | 20 | 1 mg/kg | 0.15 mg/kg | 1 | | | | | | | |

*Table continued*

**Table I.** ***(Continued).*** Details of the included trials.

| Study | Year | Number of patients | Dose of propofol | Dose of etomidate | Primary outcome, Incidence of myoclonus | | | | Other anesthesia techniques | Secondary outcome | Country | Surgery |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Total | Mild | Moderate | Severe | | | | |
| Tang et al[24] | 2018 | 60 | 1 mg/kg | 0.2 mg/kg | 19 | 8 | 5 | 6 | | SBP, DBP, HR, $SPO_2$; adverse events: injection pain, choking, vomiting respiration depression, the use of ephedrine and atropine | China | Painless colonoscopy |
| | | 60 | 0 mg/kg | 0.2 mg/kg | 37 | 10 | 9 | 18 | | | | |
| Lin[25] | 2018 | 30 | 0 mg/kg | 0.4 mg/kg | 17 | | | | | MAP, SBP, DBP, HR, adverse event; injection pain | China | General anesthesia induction |
| | | 30 | 1 mg/kg | 0.2 mg/kg | 3 | | | | | | | |
| Vikram et al[26] | 2018 | 30 | 0 mg/kg | 0.3 mg/kg | 23 | 15 | 7 | 1 | Glycopyrrolate 0.2 mg, ondansetron 4 mg fentanyl 1 ug/kg intravenously | SBP, DBP, HR, incidence of pain on injection, nausea, vomiting | India | Elective surgery under general anesthesia |
| | | 30 | 1 mg/kg | 0.2 mg/kg | 2 | 2 | 0 | 0 | | | | |
| Zhang et al[27] | 2020 | 20 | 0 mg/kg | 0.3 mg/kg | 15 | 7 | 5 | 3 | Sufentanil 0.1 ug/kg intravenously before induction | MAP, HR, $SPO_2$; adverse events: apnea, vomiting and nausea, $SPO_2$<90%, body moving | China | Painless gastrointestinal endoscopy |
| | | 20 | 0.3 mg/kg | 0.2 mg/kg | 5 | 3 | 2 | 0 | | | | |
| | | 20 | 0.6 mg/kg | 0.2 mg/kg | 2 | 2 | 0 | 0 | | | | |
| | | 20 | 0.8 mg/kg | 0.2 mg/kg | 1 | 0 | 0 | 0 | | | | |

SBP: Systolic blood pressure. DBP: Diastolic blood pressure. MAP: Mean arterial pressure. HR: Heart rate. $SPO_2$: Oxyhemoglobin saturation. RR: Respiratory rate. PONV: Postoperative nausea and vomiting.

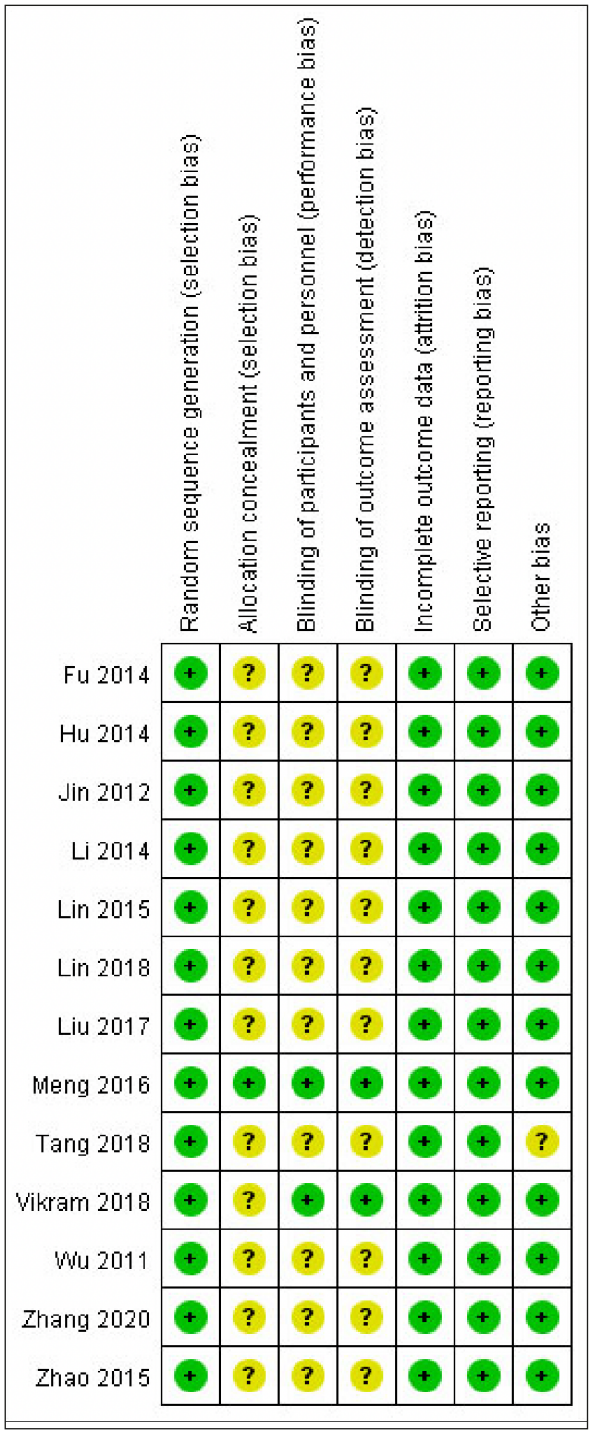


**Figure 2.** Risk of bias assessment of included studies. Green + dot, low risk of bias; yellow ? dot, unclear risk of bias.

premedications. Once deleting the studies, the heterogeneity of remaining studies was decreased ($I^2$=46.8%) and the result still showed a significant difference between the two groups in Figure 4B (RR: 4.32, 95% CI [2.71,6.89], $p$<0.0001).

### Moderate Myoclonus

Eight studies[15-17,20,22,24,26,27] included among the thirteen studies reported the moderate degree of etomidate-induced myoclonus. The incidence of mild myoclonus was 10 out of 393 (2.5%) in the propofol plus etomidate group and 76 out of 392 (19.4%) in the etomidate group, respectively. A fixed-effect model was applied for the low heterogeneity ($I^2$=12.6%). The result showed that propofol plus etomidate could significantly decrease the incidence of etomidate-induced moderate myoclonus (RR:5.4, 95% CI [3.01, 9.67], $p$<0.0001), compared with etomidate alone in Figure 4C.

### Severe Myoclonus

Eight studies[15-17,20,22,24,26,27] reported the severe degree of etomidate-induced myoclonus. The incidence of mild myoclonus was 6 of 393 (1.5%) in the propofol plus etomidate group and 41 of 392 (10.5%) in the etomidate group, respectively. There was no heterogeneity ($I^2$=0%), therefore, a fixed-effect model was used. The meta-analysis showed that co-administration of propofol and etomidate could significantly decrease the incidence of etomidate-induced moderate myoclonus (RR:4.15, 95% CI [2.11, 8.13], $p$<0.0001), compared with etomidate alone in Figure 4D.

### Recovery Time

Six studies[15,16,18,19,21,23] reported the recovery time. A random-effect model was used for the high heterogeneity ($I^2$=93.9%). The result showed that combination of propofol and etomidate could reduce the recovery time compared to etomidate alone (RR:0.80, 95% CI [0.09, 1.52], $p$=0.0270) in **Supplementary Figure 1A**.

### Sensitivity analysis

Three[16,18,21] of the six studies included may have led to heterogeneity. After removing the studies, there was no heterogeneity among the remaining studies ($I^2$=0%), a fixed-effect model was used and the result showed that no significant difference was found between the propofol plus etomidate group and etomidate group (RR: 0.06, 95% CI [-0.23, 0.36], $p$=0.6670) (**Supplementary Figure 1B).**

### Hemodynamic Parameters (MAP, HR)

Seven studies[15,20-23,26,27] described the mean arterial pressure (MAP) at 1 min after anesthesia induction, but two[21,22] of seven studies did not have exact data. Five studies[15,20,23,26,27]were included. A random-effect model was used for the moderate

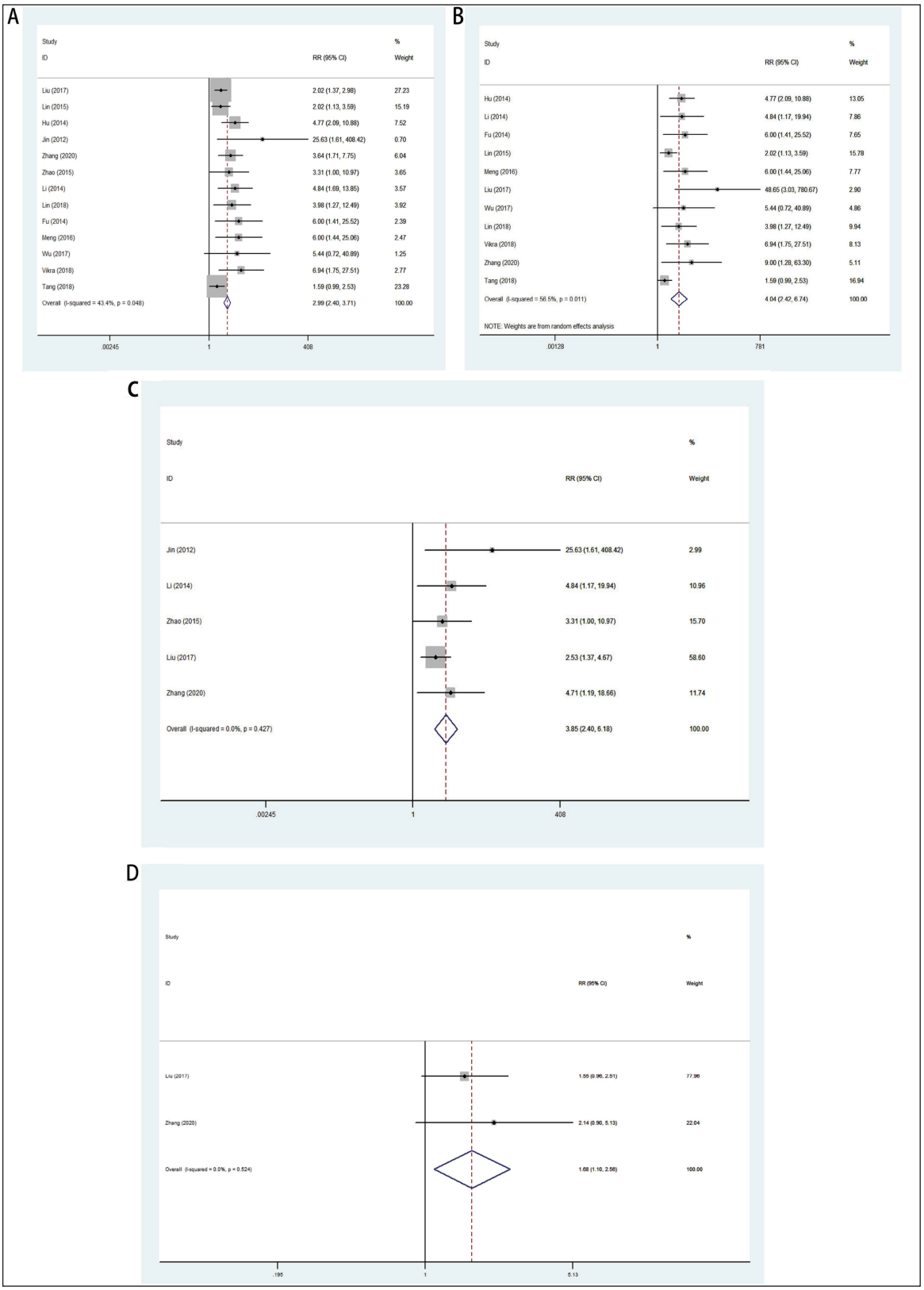


**Figure 3.** Forest plot of incidence of etomidate-induced myoclonus (**A**) combination of propofol and etomidate *vs.* etomidate alone. The dose of propofol for anesthesia induction 0.8-2 mg/kg (**B**). The dose of propofol for anesthesia induction 0.5-0.8 mg/kg (**C**). The dose of propofol for induction 0.25-0.5 mg/kg (**D**). CI indicates confidence interval.

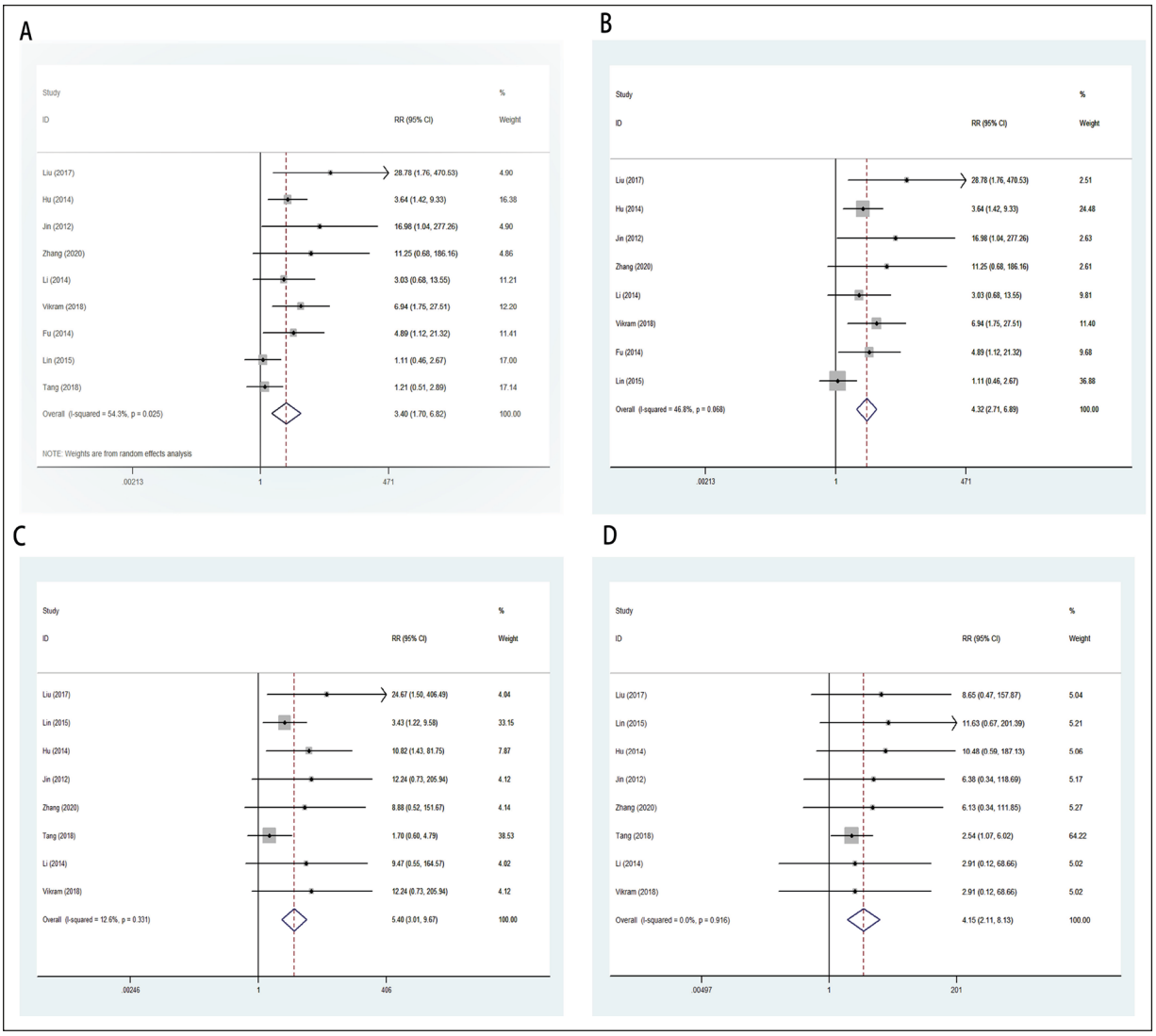


**Figure 4.** Forest plot of severity (**A**) and sensitivity analysis (**B**) of etomidate-induced myoclonus: mild myoclonus, combination of propofol and etomidate *vs.* etomidate alone. Forest plot of severity of etomidate-induced myoclonus: moderate myoclonus, combination of propofol and etomidate *vs.* etomidate alone (**C**). Forest plot of severity of etomidate-induced myoclonus: severe myoclonus, combination of propofol and etomidate *vs.* etomidate alone (**D**). CI indicates confidence interval.

heterogeneity ($I^2$=65.8%). The result (**Supplementary Figure 1C**) showed that there was no significant difference between the two groups (RR: 0.39, 95% CI [-0.01, 0.8], $p$=0.0560).

Nine studies[15,17,20-24,26,27] reported the heart rate (HR) at 1 min after anesthesia induction, but two of the studies did not have exact data[21,22]. Seven studies[15,17,20,23,24,26,27] were included. There was no heterogeneity among the study results, a fixed-effect model was used ($I^2$=0%). The result (**Supplementary Figure 1D**) showed that there was no significant difference between the two groups (RR: 0.08, 95% CI [-0.1, 0.26], $p$=0.3610).

## Adverse Events

### Pain on injection

Four studies[21,24,25,26] reported the outcome of pain on injection. A fixed-effect model was used for the low heterogeneity ($I^2$=41.5%). In **Supplementary Figure 2A**, the incidence of pain on injection was significantly higher in combination of propofol and etomidate group than that in

**Table II.** Quality assessment.

| Outcome | Limitation | Inconsistency | Indirectness | Imprecision | Publication bias | Summary in finding | | | | Quality of evidence (GRADE) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | No. participants in etomidate group | No. Participants in propofol plus etomiate group | RR (95%CI) | *p-value* for the overall effect | |
| Occurrence of etomidate-induced myoclonus | Concealment not clear in most studies | Low inconsistency | No indirectness | No serious imprecision | Yes | 602 | 603 | RR=2.99, 95% CI [2.40, 3.71] | 0.000 | ⊕⊕⊕⊖ Moderate quality |
| Incidence of etomidate-induced mild myoclonus | Concealment not clear in most studies | Moderate inconsistency | No indirectness | No serious imprecision | Not suggestive | 462 | 463 | RR:3.40, 95% CI [1.7, 6.82] | 0.001 | ⊕⊕⊕⊖ Moderate quality |
| Incidence of etomidate-induced moderate myoclonus | Concealment not clear in most studies | Low inconsistency | No indirectness | No serious imprecision | Not suggestive | 392 | 393 | RR:5.4, 95% CI [3.01, 9.67] | 0.000 | ⊕⊕⊕⊕ High quality |
| Incidence of etomidate-induced severe myoclonus | Concealment not clear in most studies | Low inconsistency | No indirectness | No serious imprecision | Not suggestive | 392 | 393 | RR:4.15, 95% CI [2.11, 8.13] | 0.000 | ⊕⊕⊕⊕ High quality |

⊕⊕⊕⊕, high quality evidence; ⊕⊕⊕⊖, moderate quality evidence; ⊕⊕⊖⊖, low quality evidence, ⊕⊖⊖⊖, very low-quality evidence. RR: relative risk; CI: confidence interval. GRADE: grading of recommendations assessment, development, and evaluation system.

etomidate group (RR: 0.47, 95% CI [0.26, 0.83], $p$=0.0100).

### Postoperative Nausea and Vomiting (PONV)

Six studies[16,21,22,24,26,27] reported incidence of PONV, and no statistical heterogeneity was found among the study results ($I^2$=0%). A fixed-effect model was used, a significantly higher incidence of PONV was found in etomidate group, when compared with co-administration of propofol and etomidate group (RR: 2.07, 95% CI [1.35, 3.17] $p$=0.0010) (**Supplementary Figure 2B**).

### Respiratory Depression/Hypoxemia

Three studies[22,24,27] described the incidence of respiratory depression/hypoxemia. No statistical heterogeneity was found among the study results ($I^2$=0%), a fixed-effect model was used. There was no significant difference in the occurrence of respiratory depression/hypoxemia between the two groups (RR: 0.37, 95% CI [0.13, 1.06], $p$=0.0650) (**Supplementary Figure 2C**).

### Publication Bias

Funnel plot for the analysis of incidence of etomidate-induced myoclonus was shown in **Supplementary Figure 2D**. Begg's test ($p$=0.0020) and Egger's test ($p$=0.0030) were used to verify the possible presence of publication bias. The result showed that publication bias existed in the analysis of the efficacy of propofol in attenuating etomidate-induced myoclonus.

### Quality of Evidence

GRADE system grades of evidence are of moderate quality for the occurrence of etomidate-induced myoclonus and the etomidate-induced mild myoclonus and high quality for etomidate-induced moderate and severe myoclonus (Table II).

## Discussion

Etomidate directly acts on GABA receptor and produces anesthesia[28]. Pain on injection, adrenal suppression and myoclonus are main complications of the drug. The former two have been resolved by Etomidate-®Lipuro[29] and synthesis of rapidly metabolized etomidate soft analogs[30]. Etomidate-induced myoclonus, a clinical concern, has not been solved. Various pretreatment therapies such as dexmedetomidine, remifentanil, lidocaine, magnesium sulfate have been reported to prevent the etomidate-related myoclonus[31,32-34]. Propofol is widely applied as an induction agent for general anesthesia and in the treatment of seizure due to its anticonvulsive properties[35]. But propofol induced generalized tonic-clonic seizure when patient was infused at low concentrations for the maintenance of anesthesia[36].

Based on the existing evidence from thirteen studies, our analysis indicated that propofol at different dose (0.25-2 mg/kg) could decrease the occurrence and severity (mild, moderate, and severe) of etomidate-induced myoclonus.

Several studies[37-39] ha been trying to explore the mechanism of etomidate induced myoclonus, such as spontaneous nerve transmissions, seizure-like activity, the depressed inhibitory circuits prior to excitatory neuronal circuits. Räth et al[40] found that etomidate can inhibit glutamate uptake by blocking the transporter protein of glutamate transporter 1 (GLT1), increasing the extracellular glutamate concentration in cultured astrocytes, which may contribute to etomidate-induced myoclonus. As we known, propofol not only potentiate inhibitory synapses but also impairs excitatory neurotransmission in the brain. Karunanithi et al[41] have provided evidence that propofol at a clinically relevant concentration (3 μM) decreases excitatory neurotransmission release of active sites at drosophila motor presynaptic terminals, and Velly et al[42] have demonstrated that propofol (5 μM) can reverse the oxygen-glucose deprivation-induced elevation of the extracellular glutamate concentrations by reducing glutamate uptake. In addition, low doses of propofol can prevent the etomidate-induced myoclonus in our analysis. In agreement with the previous results, Liu et al[22] reported that pretreatment of propofol at the low doses of 0.25-0.75 mg/kg played inhibitory role on myoclonus induced by etomidate, since propofol alone depresses the cortex inhibiting the inhibitory subcortex and promote the seizure activity of subcortical regions[43]. Additionally, the NMDA-mediated increases in intracellular calcium in hippocampal Cornus Ammonis 1 (CA1) pyramidal cell layer was not completely inhibited by propofol at low concentrations[44,45]. Etomidate alone induces interictal seizure-like event in the neocortex[7] and enhances inhibitory synaptic transmission in hippocampal CA1 pyramidal neurons[46]. When etomidate combined with propofol, the main effect is synergistic with limited complications.

In our analysis, recovery time was reported in six studies[15,16,18,19,21,23], the initial result of integrated data showed that etomidate could prolong the recovery time, compared with propofol plus etomidate. However, sensitivity analysis was applied for the high heterogeneity ($I^2$=93.9%). Three studies[16,18,21] might lead to the high heterogeneity. The elderly (52-79 years) was included in two studies[18,21] and the young (17-32 years) were included in one study[16], whereas adult patients (18-75 years) were included in other three studies[15,19,23]. After removing three studies[16,18,21] with the elderly and young patients, no heterogeneity and no difference was found between the two groups.

Etomidate is known for the side effect of PONV, which is higher than propofol[47]. In our study, combination of propofol and etomidate decreased the incidence of PONV, compared to etomidate alone, which is similar to the results of preliminary meta-analysis[9] with eleven trails included. Furthermore, propofol is associated with side effect of pain on injection[48], respiratory depression[49] and cardiovascular depression with the hypotension[50] for anesthesia induction. In our analysis, on one hand, there was no difference between combination of propofol and etomidate and etomidate alone in the incidence of respiratory depression, MAP and HR at 1 min after anesthesia. This revealed that combination of propofol and etomidate weakened the disadvantages of propofol. On the other hand, co-administration of propofol and etomidate increased the incidence of pain on injection, compared with etomidate alone, which was different from the result of Chen's meta-analysis[9]: compared with etomidate alone, the combined use of propofol and etomidate showed no significant difference in injection pain. This could be due to the fact that only four studies[21,24-26] were included in our meta-analysis in pain on injection.

To the best of our knowledge, this is the first meta-analysis presenting the effect of propofol on prevention of etomidat-related myoclonus.

### Limitations

However, there are some limitations in our study. First, according to the results of Begg's test and Egger's test, our analysis is compatible with publication bias. This phenomenon might occur in the absence of trials with negative results, because the comparison was conducted between the pharmacological intervention group and the control group. Second, 12 out of 13 studies are from China, thus data from English language publications may be deficient. Third, the sample size and quality of included studies are associated with limitations. Therefore, more large-sample, high-quality studies will be needed to confirm the present results.

## Conclusions

In summary, the meta-analysis currently generates the evidence of combination of propofol with dose of 0.25-2 mg/kg and etomidate can alleviate occurrence and the severity of etomidate-induced myoclonus, with decreased incidence of PONV and comparative influence on the side effects of hemodynamic and respiratory depression of patients in comparison with etomidate alone.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Funding

None.

### Ethics Approval

No patients or members of the public were involved in the present study. No ethical approval and patient consent were required.

### Informed Consent

Not applicable.

### Availability of Data and Material

Data are available from the corresponding author on a reasonable request.

### Authors' Contribution

Yan Feng: helped design, conduct, analyze, write and revise the study. Xiao-bo Chen: helped conduct, analyze, and revise the study. Yu-lin Zhang: helped conduct, analyze the study. helped analyze, write and revise the study. Pan Chang: helped conduct, analyze, revise the study. Wensheng Zhang: helped design, conduct, analyze, write and revise the study.

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