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Safety and efficacy of combined use of propofol and etomidate for sedation during gastroscopy
Systematic review and meta-analysis

Lingyuan Chen, BS[a], Xueyan Liang, MM[a], Xinmei Tan, MM[b], Haibin Wen, MM[c], Junsong Jiang, MM[d,*], Yan Li, MM[a,*]

Abstract

Background: Sedation with etomidate or propofol alone during gastroscopy has many side effects. A systematic review and meta-analysis were conducted to evaluate the safety and efficacy of the combined use of propofol and etomidate for sedation during gastroscopy.

Methods: PubMed, Embase, Medline (via Ovid SP), Cochrane library databases, CINAHL (via EBSCO), China Biology Medicine disc (CBMdisc), Wanfang, VIP, and China National Knowledge Infrastructure (CNKI) databases were systematically searched. We included randomized controlled trials (RCTs) comparing the combined use of propofol and etomidate vs etomidate or propofol alone for sedation during gastroscopy. Data were pooled using the random-effects models or fixed-effect model based on heterogeneity.

Results: Fifteen studies with 2973 participants were included in the analysis. Compared to propofol alone, the combined use of propofol and etomidate possibly increased recovery time (SMD = 0.14, 95% CI = 0.04–0.24; P = .005), and the risk for myoclonus (OR = 3.07, 95% CI = 1.73–5.44; P < .001), injection pain, and nausea and vomiting. Furthermore, compared to propofol alone, the combination of propofol and etomidate produced an apparent beneficial effect for mean arterial pressure (MAP) after anesthesia (SMD = 1.32, 95% CI = 0.38–2.26; P = .006), SPO_2 after anesthesia (SMD = 0.99, 95% CI = 0.43–1.55; P < .001), apnea or hypoxemia (OR = 0.16, 95% CI = 0.08–0.33; P < .001), injection pain, and body movement. Further, compared to etomidate alone, the combination of propofol and etomidate reduced the risk for myoclonus (OR = 0.15, 95% CI = 0.11–0.22; P < .001), body movement, and nausea and vomiting.

Conclusion: The combination of propofol and etomidate might increase recovery time vs that associated with propofol, but it had fewer side effects on circulation and respiration in patients undergoing gastroscopy. The combined use of propofol and etomidate can improve and produce an apparent beneficial effect on the adverse effects of propofol or etomidate alone, and it was safer and more effective than propofol or etomidate alone.

Abbreviations: CI = confidence interval, HR = heart rate, MAP = Mean arterial pressure, OR = odds ratio, RCTs = randomized controlled trials, SMD = standardized mean differences, SPO_2 = pulse oxygen saturation.

Keywords: anesthesia, etomidate, gastroscopy, meta-analysis, propofol

[a] Department of Pharmacy, [b] Department of anesthesiology, [c] Department of Nephrology, [d] Department of Reproductive Medicine, The People's Hospital of Hechi, Hechi, PR China.

[*] Correspondence: Junsong Jiang, Master of Medicine, Department of Reproductive Medicine, The People's Hospital of Hechi, Hechi, PR China (e-mail: junsongjiang@hotmail.com); Yan Li, Master of Medicine, Department of Pharmacy, The People's Hospital of Hechi, Hechi, PR China. (e-mail: liyan20102010@outlook.com).

1. Introduction

Gastroscopy is a non-traumatic invasive procedure used for the diagnosis of gastrointestinal pathology and treatment of gastrointestinal hemorrhage, polyps, and corpus alienum.[1] It is frequently performed with anesthesia to ensure patient comfort. The procedure requires that the anesthetic regimen being used provide rapid induction, sufficient anesthesia, hemodynamic stability, quick recovery and minimal side effects. In many countries, gastroscopy is also performed in patients under sedation rather than anesthesia. Patients who receive gastroscopy frequently have cardiovascular or respiratory disease and other complications, which makes safe and efficient administration of anesthesia difficult while maintaining stable hemodynamics and respiration. It should be one of the key factors to understanding how to maintain hemodynamic stability and spontaneous respiration in patients during gastroscopy. To guarantee successful outcomes of gastroscopy, the choice of an appropriate anesthetic agent for sedation is important.[2]

The first point to consider in anesthetic agent selection is a pharmacokinetic profile with a short half-life and a rapid onset of action. In this respect, propofol is one of the most useful anesthetic agents for sedation during many endoscopic procedures,[3–5] including gastroscopy.[6,7] Many types of anesthetic

agents have been used for gastroscopy, such as propofol,[6,8] etomidate,[7] remifentanil,[9] and midazolam.[10] Propofol has particular characteristics such as fast onset and short duration of action, short half-life, rapid achievement of the sedative depth, and short recovery time,[11,12] and it is recognized as a classical sedative. When propofol is used alone as a sedative for gastroscopy, it had many side effects,[3,4,13] the most important of which are apnea or hypoxemia and cardiovascular events. These side effects appear to be dose and injection speed related[14] and are potentially serious complications. The US Food and Drug Administration recommends that propofol should only be administered by persons trained in the administration of general anesthesia.[15]

Etomidate is a short-acting intravenous hypnotic. It has particular characteristics such as a rapid onset of action, with advantages in terms of hemodynamics and respiration, compared to propofol.[16–18] It has little effect on heart rate and blood pressure, and can be safely used in patients at risk of acute cardiovascular instability.[19] In addition, etomidate plays an important role in emergency medicine as an adjunct to rapid sequence intubation,[20,21] in patients with bronchospasms[22] or in those with intracranial pathologies in which hypotension must be avoided.[23] Its rapid onset and recovery time and stable hemodynamic and respiratory effects may facilitate optimal and safe conditions for procedural sedation in mergency medicine.[24] Compared to propofol, etomidate showed fewer side effects on histamine release, and allergic reactions.[19] However, there are also adverse effects of etomidate after an operation, such as myoclonus,[25] nausea and vomiting.[26] Interestingly, propofol inhibits myoclonus,[27] nausea, and vomiting[27] caused by etomidate.

Considering the previously reported evidence about these complementary effects of propofol and etomidate, the combined use of propofol and etomidate may be a promising approach that could replace propofol or etomidate alone in gastroscopy. However, there is a lack of a high-quality meta-analysis concerning the safety and efficacy of the combined use of propofol and etomidate for gastroscopy. The aim of the study, therefore, was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the safety and efficacy of the combined use of propofol and etomidate for patients undergoing gastroscopy.

2. Materials and methods

2.1. Search strategy

The study was approved by the ethics institutional review board of the The People's Hospital of Hechi. PubMed, Embase, Medline (via Ovid SP), Cochrane library databases, CINAHL (via EBSCO), China Biology Medicine disc (CBMdisc), China National Knowledge Infrastructure (CNKI), Wanfang, VIP databases up to 18 August 2018 were systematically searched. The following search terms were used: 'etomidate', 'radenarkon', 'hypnomidate', 'propofol', 'disoprofol', '2,6-diisopropylphenol', '2,6-bis(1-methylethyl)phenol', 'disoprivan', 'fresofol', 'gastroscopy', 'gastroscopies', 'gastroscopic surgical procedures', and 'gastroscopic surgery'. The search strategy is shown in Table S1, http://links.lww.com/MD/C986. No language restriction was imposed. The reference lists of all retrieved articles were reviewed to identify additional articles missed by using these search terms. The authors approved all the enrolled studies.

2.2. Inclusion criteria

Studies meeting the following criteria were included:

1. population: patients in whom gastroscopy was indicated;
2. intervention: etomidate plus propofol or propofol plus etomidate;
3. comparison: etomidate or propofol alone;
4. outcome: recovery time, mean arterial pressure (MAP), hypotension, bradycardia, heart rate (HR), pulse oxygen saturation (SPO$_2$), apnea or hypoxemia, myoclonus, nausea and vomiting, body movements, and injection pain;
5. design: RCTs.

2.3. Exclusion criteria

The exclusion criteria were

1. reviews, nonclinical studies and case observations;
2. non-RCTs;
3. reduplicated studies;
4. studies in which control groups received etomidate or propofol alone or treatment groups did not receive etomidate plus propofol or propofol plus etomidate;
5. studies in which control groups received the intervention that treatment groups did not receive;
6. improper outcome measures;
7. meta-analysis, case reports, editorials, and meeting abstracts.

2.4. Selection of studies and data extraction

A comprehensive search of databases was performed by 2 researchers (Chen and Liang). The researchers deleted duplicate records, screened the titles and abstracts for relevance, and identified each as excluded or requiring further assessment. We reviewed the full-text articles designated for inclusion and manually checked the references of the retrieved articles and previous reviews to identify additional eligible studies. Discrepancies were resolved by consensus. The following data were extracted from each study: first author, year of publication, number of patients, interventions, comparisons, and outcomes.

2.5. Risk of bias assessment

Two reviewers (Chen and Liang) independently evaluated the methodological quality of the identified studies. The "risk of bias tool" from the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 was used to assess methodological quality.[28] In terms of the assessment criteria, each study was rated and assigned to one of the three following risks of bias: low: if all quality criteria were adequately met, the study was deemed to have a low risk of bias; unclear: if one or more of the quality criteria were only partially met or unclear, the study was deemed to have a moderate risk of bias; or high: if one or more of the criteria were not met, or not included, the study was deemed to have a high risk of bias.[29]

2.6. Statistical analysis

Data were analyzed using the Review Manager 5.1.0. statistical package (Cochrane Collaboration Software). Continuous outcomes were expressed as standardized mean differences (SMD) with 95% confidence intervals (CI). Dichotomous outcomes were

expressed as odds ratio (OR) with 95% CI. Test of heterogeneity was conducted with the I^2 test and Q statistic which is distributed as a χ^2 variate under the assumption of homogeneity of effect sizes.[30] A value of I^2 greater than 50% was assumed to indicate substantial heterogeneity and the potential sources of heterogeneity were sought, such as clinical heterogeneity and methodological heterogeneity.[31] If substantial heterogeneity occurred ($I^2 > 50\%$ or $P < .05$), a random-effect model was used to calculate the pooled SMD or OR. Publication/reporting biases were visually assessed using funnel plots. If there was no observed heterogeneity, the fixed-effect model was chosen. The subgroup analyses were performed based on the etomidate or propofol injection sequence.

3. Results

3.1. Study identification and selection

A total of 400 records were retrieved from the initial database search. After removing duplicate articles, 156 records were eligible. Based on the inclusion and exclusion criteria, 116 articles were excluded after a simple reading of the titles and abstracts of the articles. The remaining 39 full-text articles were assessed for eligibility. Furthermore, studies with not a relevant study design, non-RCTs, meta-analysis, studies that reported only combination treatment, and studies with combination specifics were excluded. Finally, a total of 15 RCTs studies were included in the meta-analysis.[7,27,32–44] The selection process is shown in Fig. 1.

3.2. Study characteristics

The basic characteristics of the included studies are listed in Table 1 and Table 2. Fifteen RCTs studies involving 2973 participants were included in the analysis. These studies were published from 2006 to 2018. The number of participants in the studies ranged from 80 to 400.

Among the included trials, all of the included studies were conducted in China. One out of the 15 RCTs compared the combined use of propofol and etomidate with etomidate or propofol alone.[7] Four RCTs compared etomidate plus propofol with etomidate or propofol alone.[32,33,39,44] Five RCTs compared propofol plus etomidate with etomidate or propofol alone.[34–36,38,41] Three RCTs compared propofol plus etomidate with propofol alone.[27,37,43] The remaining 2 trials compared propofol plus etomidate with etomidate alone.[40,42]

3.3. Risk of bias assessment

The outcomes of the risk of bias are summarized in Figure 2A and B. Most of the included RCTs were assessed to be of a low methodological quality. One used a random digital method involving the use of computers,[27] 1 used computer generated random numbers table[7], 4 RCTs used a random number table.[32,36,38,39] One RCT did not mention whether a random was used.[44] The rest did not provide any detailed information. Therefore, we were unable to assess the quality of the random
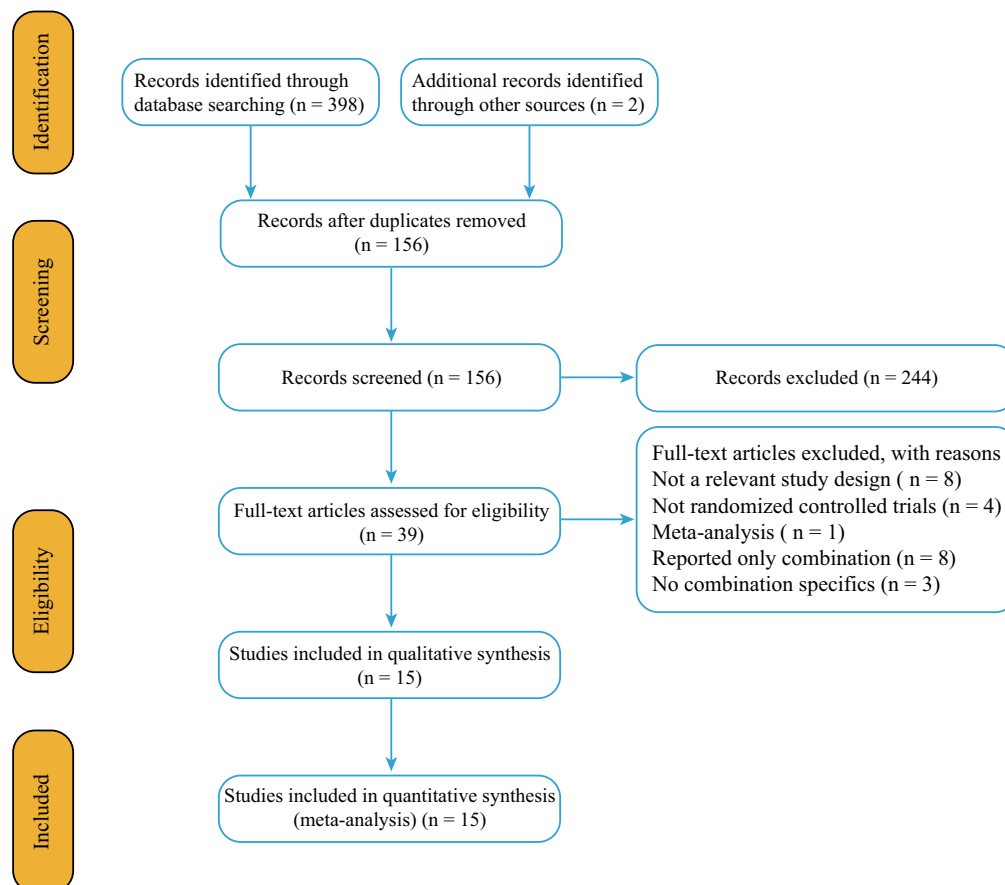

Figure 1. Selection process for the studies included in the meta-analysis.

Table 1

The characteristics of the included studies.

Author (year)	Sample size				Outcomes
	Treatment group		Control group		
	P + E	E + P	P	E	
Chen, 2012	–	30	30	30	a, b, c, e, h, i, j, k
Chen, 2017	–	60	60	60	a, b, d, e, f, g, h, j
Gao, 2006	80	–	80	80	a, c, h, i
Guo, 2014	40	–	40	40	b, c, e, h, i, k
Guo, 2017	60	–	60	60	d, e, i, j, k
Lei, 2015	60	–	60	–	c, h
Liu, 2017	218	–	73	72	e, i, j
Meng, 2016	50	50	50	50	a, d, e, f, g, i, j, k
Song, 2018	–	40	40	40	a, b, c, e, h, i, j, k
Wang, 2013	40	–	–	40	a, b, c, e, h, i
Xu, 2015	100	–	100	100	a, b, e, h, k
Zhang, 2017	100	–	–	100	a, d, e, g, k
Zhou, 2016	200	–	200	–	a, d, e, f, g, i, k
Zhu, 2012	100	–	100	–	a, d, e, i
Zhu, 2015	–	60	60	60	a, c, e, h, i, j, k

P = propofol; E = etomidate; –: no report; LP = low-dose propofol; MP = middle-dose propofol; HP = high-dose propofol.
[Outcomes]: a: recovery time; b: MAP; c: SPO$_2$; d: apnea or hyoxemia; e: myoclonus; f: hypotension; g: bradycardia; h: heart rate; i: nausea vomiting; j: body movements; k: injection pain.

Table 2

Intervention and comparison of the included studies.

Author (yr)	Intervention	Comparison
Chen, 2012	Etomidate (0.25 mg/kg) plus propofol (0.6–0.8 mg/kg) induction, maintained with etomidate (0.05–0.1 mg/kg).	Propofol (0.6–0.8 mg/kg) induction, maintained with propofol (0.5–1.0 mg/kg).
Chen, 2017	0.1% etomidate plus 0.5% propofol 50 mL/h induction by micro-pump.	0.5% propofol 50 mL/h induction by micro-pump 0.1% etomidate 50 mL/h induction by micro-pump.
Gao, 2006	Propofol (0.8 mg/kg) plus etomidate (0.16 mg/kg) induction, maintained with etomidate (1–2 mL).	Propofol (1.6 mg/kg) induction, maintained with propofol (1–3 mL). Etomidate (0.2 mg/kg) induction, maintained with propofol (1–2 mL).
Guo, 2014	1% propofol (0.125–0.17 mL/kg) plus 0.2% etomidate (0.025–0.03 mg/kg) induction.	Propofol (1.5–2 mg/kg) induction, maintained with propofol (40–50 mg). Etomidate (0.2–0.3 mg/kg) induction, maintained with propofol (5–7 mg).
Guo, 2017	Propofol (0.075 mL/kg) plus etomidate (0.075 mg/kg) induction.	Propofol (1.5 mg/kg) induction. Etomidate (0.2 mg/kg) induction.
Lei, 2015	Propofol (0.9 mL/4 s) plus etomidate (0.1 mL/4 s) induction.	Propofol (1 mL/4 s) induction.
Liu, 2017	LPE group received propofol (0.25 mg/kg) plus etomidate (0.2 mg/kg). MPE group received propofol (0.5 mg/kg) plus etomidate (0.2 mg/kg). HPE group received propofol (0.75 mg/kg) plus etomidate (0.2 mg/kg).	Propofol (2 mg/kg) induction. Etomidate (0.3 mg/kg) induction.
Meng, 2016	Propofol (0.75–1 mg/kg) plus etomidate (0.075–0.1 mg/kg) induction, maintained by propofol 2 mg/(kg h) plus etomidate 0.2 μg/(kg×·h) pump infusion, respectively. Etomidate (0.075–0.1 mg/kg) plus propofol (0.75–1 mg/kg) induction, maintained by propofol 1 mg/(kg h) plus etomidate 0.2 μg/(kg·h) pump infusion, respectively.	Propofol (1.5–2.0 mg/kg) induction, maintained by propofol 4 mg/(kg h) pump infusion. Etomidate (0.15–0.2 mg/kg) induction, maintained by etomidate 0.4 μg/(kg·h) pump infusion.
Song, 2018	Propofol (1 mg/kg) plus etomidate (0.2 mg/kg) induction.	Propofol (2 mg/kg) induction. Etomidate (0.3 mg/kg) induction.
Wang, 2013	Propofol (0.06 mg/kg) plus etomidate (0.15–0.3 mg/kg) induction.	Etomidate (0.1–0.3mg/kg) induction.
Xu, 2015	0.1% propofol (0.1 mL/kg) plus etomidate (0.1 mL/kg) induction, 1 mL/5s.	0.1% propofol (2 mL/kg) induction. Etomidate (0.2 mL/kg) induction.
Zhang, 2017	Propofol (0.8 mg/kg) plus etomidate (0.15 mg/kg) induction, maintained by etomidate (0.05 mg/kg).	Etomidate (0.2 mg/kg) induction, maintained by etomidate (0.05 mg/kg).
Zhou, 2016	1% propofol (0.5 mg/kg) plus 2% etomidate (0.1 mg/kg) induction, maintained by 1% propofol (5–10 mg) plus 2% etomidate (1–2 mg).	1% propofol (1 mg/kg) induction, maintained by 1% propofol (10–20 mg).
Zhu, 2012	Propofol (0.8 mg/kg) plus etomidate (0.2 mg/kg) induction, maintained by propofol (0.5 mg/kg).	Propofol (1.5 mg/kg) induction, maintained by propofol (0.5 mg/kg).
Zhu, 2015	1% propofol (3–5 mL) plus 0.2% etomidate (3–5 mL) induction in 40–60 s.	1% propofol (6–10 mL) induction in 40–60 s. 0.2% etomidate (6–10 mL) induction in 40–60 s.
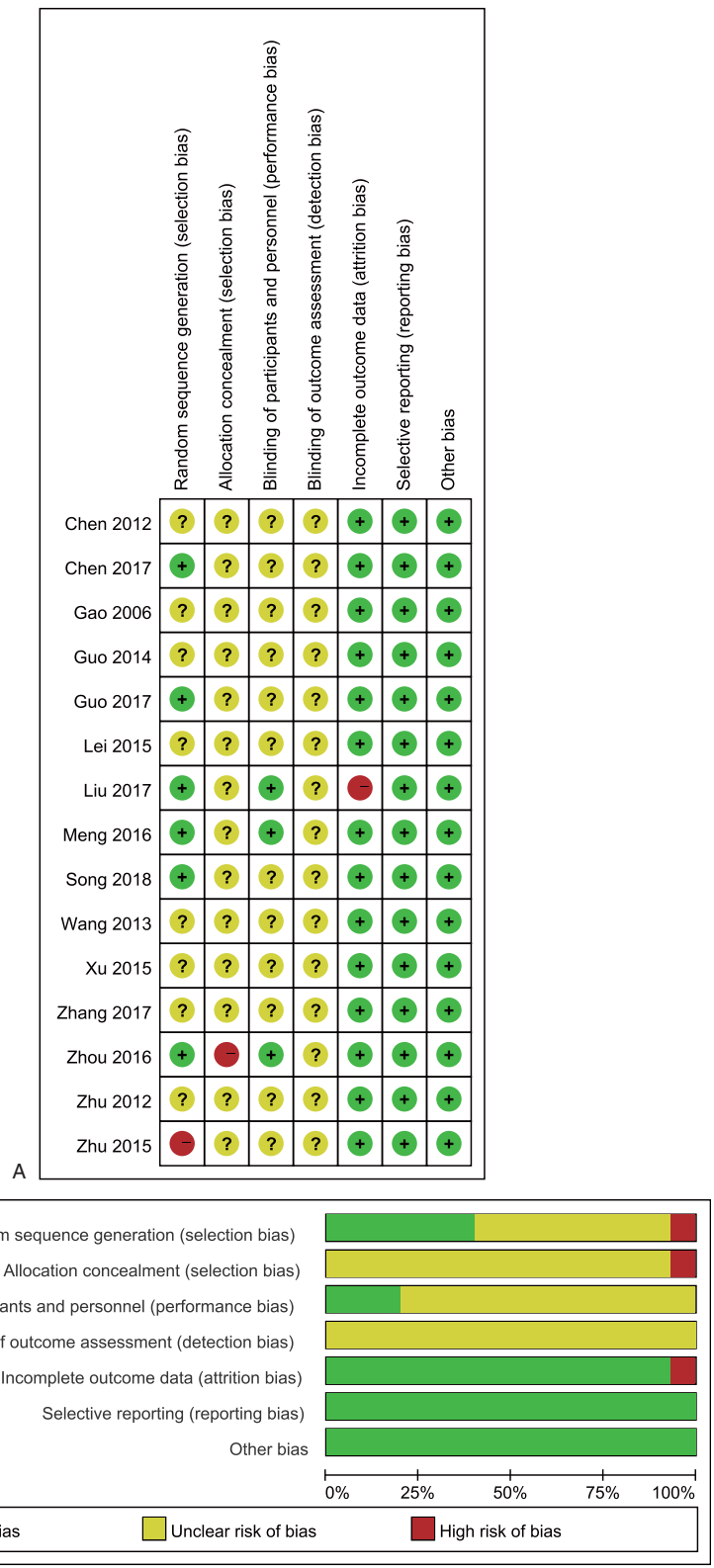
Figure 2. Methodological quality assessment of the risk of bias for each included study. (A) Risk of bias summary; (B) risk of bias graph.

sequence generation methods. Allocation concealment was not mentioned in any trial; however, in one single-blind trial, assignments could possibly be foreseen and thus selection bias might have been introduced.[27] Among the trials included, 2 out of the 15 RCTs were conducted double-blind,[7,38] and 2 were conducted single-blind.[27,34] However, the remaining trials did not provide any detailed information about the blinding of participants and personnel, and the blinding of outcome

assessment was not conducted in any trial. Besides, all studies did not have selective reporting bias, and no articles had incomplete outcome data and selective reporting. It is necessary to conduct subgroup analyses, due to the injection sequence of propofol and etomidate.

3.4. Primary outcomes: recovery time

Eleven studies including a total of 2190 patients provided data on recovery time. Nine studies including a total of 1490 patients provided data for the comparison of the use of propofol alone with that for the combined use of propofol and etomidate, and 8 studies including 1050 provided data for the comparison of the use of etomidate alone with that for the combined use of propofol and etomidate, in detail.

Compared with propofol alone, co-administration of propofol and etomidate increased the recovery time of patients undergoing gastroscopy, but subgroup analyses showed no significant difference between propofol plus etomidate and propofol alone. The test for heterogeneity of 11 studies demonstrated no heterogeneity, and the fixed-effect model was used. Based on our analysis, the pooled estimate of SMD was 0.14, and the 95% CI was 0.04–0.24 ($P = .005$) (Fig. 3A). The result suggested that compared to propofol alone, the combination of propofol and etomidate increased the recovery time of patients undergoing gastroscopy.
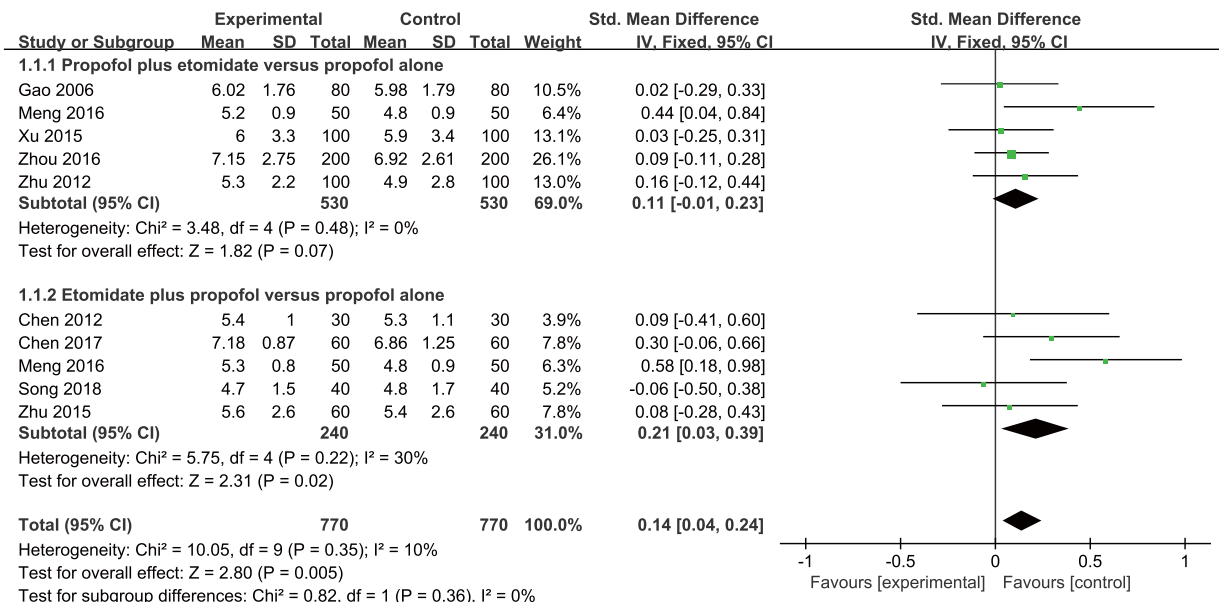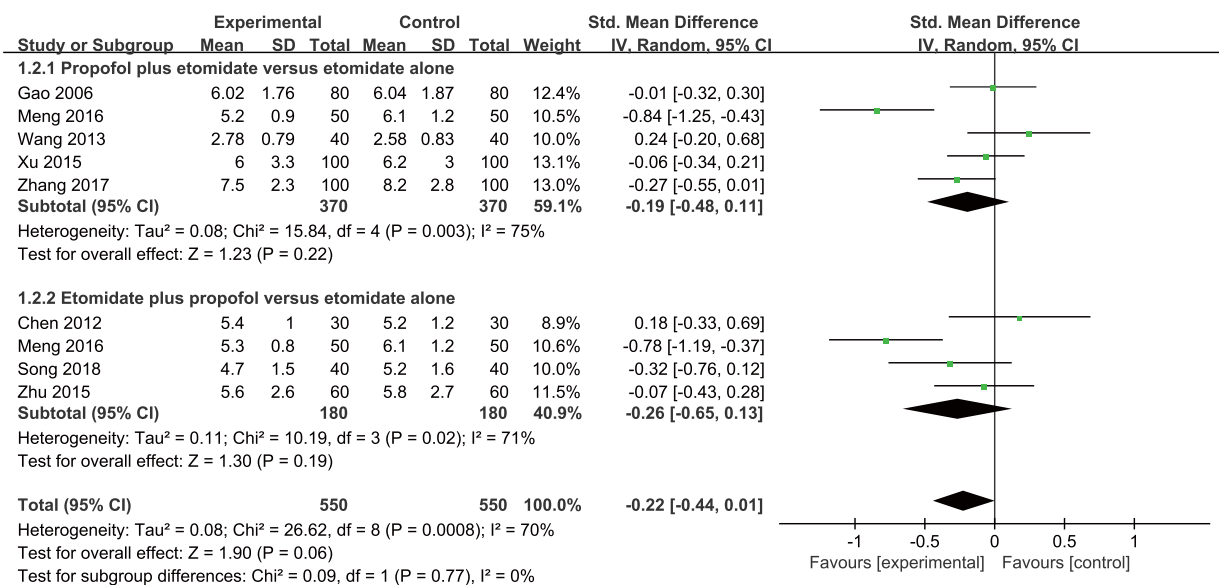
Figure 3. Meta-analysis of the of recovery time (min). (A) Recovery time of patients received co-administration of propofol and etomidate vs propofol alone, fixed-effect model; (B) recovery time of patients received co-administration of propofol and etomidate vs etomidate alone, random-effect model.

On the other hand, the pooled estimate of the 8 RCTs included suggested that no significant difference was found between propofol plus etomidate or etomidate plus propofol and etomidate alone (SMD = −0.22; 95% CI, −0.44–0.01; P = .06). Heterogeneity noted in the efficacy rate of the combined use of propofol and etomidate between etomidate alone ($\chi^2 = 26.62$, $P < .001$, $I^2 = 70\%$) (Fig. 3B). There was significant heterogeneity existed for the recovery time of the combined use of propofol and etomidate vs etomidate alone. When we considered the subgroup analysis based on injection sequence of propofol and etomidate, there was still significant heterogeneity ($I^2 > 60\%$). When we performed a sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity, $I^2 > 50\%$ indicated heterogeneity still existing. These results showed that combination of propofol and etomidate was no significant difference of recovery time when comparing etomidate alone. These results suggested that etomidate plus propofol might be an increased recovery time of patients undergoing gastroscopy. For compared with etomidate alone, patients treated with the combined use of propofol and etomidate showed no significant difference of recovery time.

3.5. On circulation system

Six studies totaling 890 patients provided data on MAP. The time point of MAP was determined at 0 to 2 minutes after the patients received anesthetics in different included studies. Following the treatment of the combined use of propofol and etomidate vs propofol alone, there was a significant difference of MAP after the patients received anesthetic (SMD = 1.32; 95% CI, 0.38–2.26; P = .006; Fig. 4A) compared with propofol alone. There was significant heterogeneity existed for MAP after the patients received co-administration of propofol and etomidate vs propofol alone ($\chi^2 = 27.07$, $P < .001$, $I^2 = 85\%$). Therefore, a random-effect model was adopted for statistical analysis.

On other hand, there was no significant difference of MAP after the patients received combination of propofol and etomidate vs etomidate alone (SMD = −0.02; 95% CI, −0.19–0.16; P = .83; Fig. 4B). The test for heterogeneity of this comparison demonstrated no heterogeneity, and the fixed-effect model was performed.

These results suggest that co-administration of propofol and etomidate had few effects on MAP of patients undergoing gastroscopy and was safer and more effective compared to
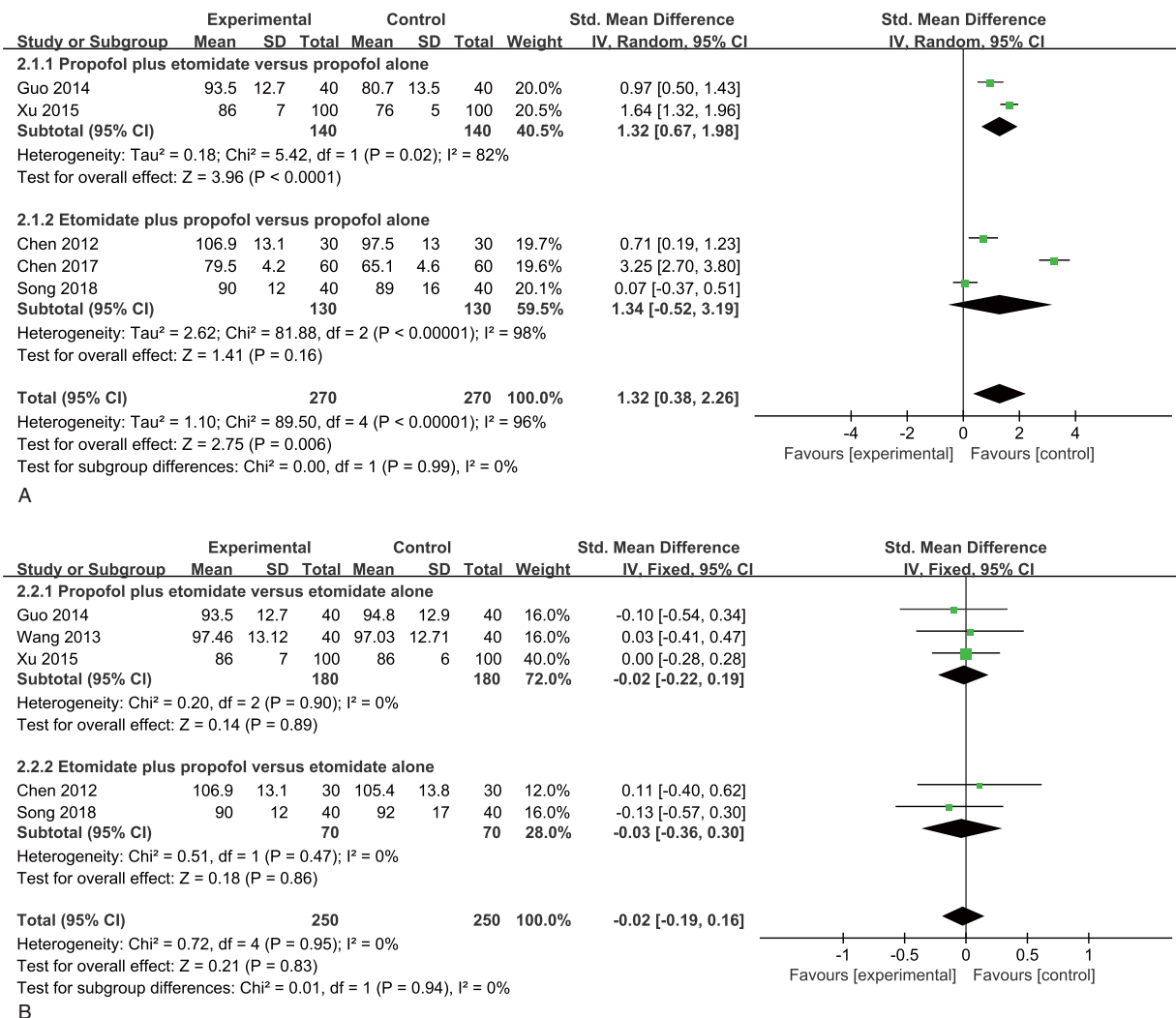
Figure 4. Meta-analysis of the MAP (mmHg). (A) MAP after the patients received co-administration of propofol and etomidate vs propofol alone, random-effect model; (B) MAP after the patients received co-administration of propofol and etomidate vs etomidate alone, fixed-effect model.

propofol alone. Etomidate is associated with hemodynamic stability, which is similar to co-administration of propofol and etomidate. In addition, the results show that a combination of etomidate and propofol can result in favorable hemodynamic stability.

Three studies totaling 780 patients provided data on hypotension after the patients received anesthetic. The combined use of propofol and etomidate was associated lower risk of hypotension compared with propofol alone (OR=0.05, 95% CI=0.01–0.19; $P < .001$; with significant heterogeneity, $\chi^2 = 14.23$, $P = .003$, $I^2 = 79\%$; Fig. S1A, http://links.lww.com/MD/C986). Four studies totaling 980 patients provided data on bradycardia after the patients received anesthetic. The combined use of propofol and etomidate was associated lower risk of bradycardia compared with propofol alone (OR=0.53, 95% CI=0.31–0.89; $P = .02$; Fig. S2A, http://links.lww.com/MD/C986), without heterogeneity. The combined use of propofol and etomidate showed no difference in hypotension and bradycardia with etomidate alone (OR=1.09, 95% CI=0.48–2.47; $P = .84$, Fig. S1B, http://links.lww.com/MD/C986; OR=0.84, 95% CI=0.37–1.91; $P = .68$, Fig. S2B, http://links.lww.com/MD/C986).

Nine studies totaling 1430 patients provided data on heart rate (HR). The time point of HR was determined at 0 to 2 minutes after the patients received anesthetics in different included studies. The combined use of propofol and etomidate was associated with SMD of 0.39 (95% CI=−0.06–0.83; $P = .09$; Fig. S3A, http://links.lww.com/MD/C986) and SMD of 0.08 (95% CI=−0.05–0.22; $P = .23$; Fig. S3B, http://links.lww.com/MD/C986) for HR after the patients received anesthetic compared with propofol (with significant heterogeneity, $\chi^2 = 76.98$, $P < .001$, $I^2 = 91\%$; Fig. S3A, http://links.lww.com/MD/C986) or etomidate alone, respectively. Compared to propofol or etomidate alone, the combined use of propofol and etomidate showed no difference in HR.

3.6. On respiration system

Six studies including a total of 950 patients provided data on SPO_2. The time point of SPO_2 was determined at 0 to 2 minutes after the patients received anesthetics in different included studies. Following co-administration of propofol and etomidate vs propofol alone, there was significant difference in SPO_2 after the patients received anesthetics (SMD=0.99, 95% CI=0.43–1.55; $P < .001$; Fig. 5A), with high heterogeneity among these studies ($\chi^2 = 52.67$, $P < .001$, $I^2 = 91\%$).

On the other hand, there was no significant difference in SPO_2 after the patients received treatment with the co-administration of propofol and etomidate vs etomidate alone (SMD=−0.09, 95% CI=−0.16–0.34; $P = .49$; Fig. 5B). The test for heterogeneity of this comparison demonstrated no heterogeneity, and the fixed-effect model was used.

These results show that the combined use of propofol and etomidate causes minimal respiratory depression vs propofol alone, preserves spontaneous respirations in patients undergoing gastroscopy. These results showed that the combined use of propofol and etomidate and etomidate or propofol alone have the same effect on HR.

3.7. Adverse events

Six studies including a total of 1420 patients provided data on apnea or hypoxemia. Compared with propofol alone, the combined use of propofol and etomidate was associated with significantly reduced apnea or hypoxemia; the pooled estimate of OR was 0.16, and the 95% CI was 0.08–0.33. ($P < .001$) (Fig. 6A). However, there was no significant difference between the combined use of propofol with etomidate and etomidate alone (OR=1.18, 95% CI=0.53–2.59; $P = .69$; Fig. 6B). These results showed that co-administration of propofol and etomidate had fewer effects on respiration in patients undergoing gastroscopy than did propofol alone, and the treatment was as safe as etomidate alone.

Thirteen studies including a total of 2513 patients provided data on myoclonus. Based on our analysis of the combined use of propofol and etomidate vs propofol alone, the pooled estimate of OR was 3.07 and the 95% CI was 1.73–5.44 ($P < .001$) (Fig. 7A). This revealed that the combined use of propofol and etomidate might increase the risk for myoclonus-realted adverse events in patients undergoing gastroscopy. On the other hand, compared to etomidate alone, the combined use of propofol and etomidate was associated with significantly reduced myoclonus in patients undergoing gastroscopy (OR=0.15, 95% CI=0.11–0.22; $P < .001$; Fig. 7B). These results showed that co-administration of propofol and etomidate had few effects on myoclonus in patients undergoing gastroscopy than did etomidate alone; however, it was not safer than propofol alone.

Eleven studies including a total of 2073 patients provided data on nausea and vomiting. Compared to propofol alone, the combined use of propofol and etomidate possibly increased the risk of nausea and vomiting in patients undergoing gastroscopy (OR=1.46, 95% CI=1.04–2.03; $P = .03$; Fig. S4A, http://links.lww.com/MD/C986) without heterogeneity. On the other hand, compared to etomidate alone, the combined use of propofol and etomidate possibly reduced the risk of nausea and vomiting in patients undergoing gastroscopy (OR=0.25, 95% CI=0.12–0.54; $P < .001$; Fig. S4B, http://links.lww.com/MD/C986). According to the χ^2 and I^2 analysis, heterogeneity was observed between 2 groups ($\chi^2 = 21.55$, $P = .01$, $I^2 = 58\%$; Fig. S4B, http://links.lww.com/MD/C986).

Eight studies include a total of 1413 patients provided data on body movement. Compared to propofol or etomidate alone, the combined use of propofol and etomidate was associated with significantly reduced body movement (OR=0.51, 95% CI=0.34–0.77; $P = .001$; Fig. S5A, http://links.lww.com/MD/C986; OR=0.28, 95% CI=0.16–0.50; $P < .001$; Fig. S5B, http://links.lww.com/MD/C986). According to the χ^2 and I^2 analyses, heterogeneity was observed between etomidate alone and combination treatment ($\chi^2 = 16.84$, $P = .03$, $I^2 = 52\%$; Fig. S5A, http://links.lww.com/MD/C986). This finding revealed that compared to propofol or etomidate alone, the combined use of propofol and etomidate causes few side effects on body movement in patients undergoing gastroscopy.

Nine studies including 1790 patients provided data on injection pain. Compared to propofol alone, the combined use of propofol and etomidate was associated with significantly reduced injection pain (OR=0.14, 95% CI=0.07–0.26; $P < .001$; Fig. S6A, http://links.lww.com/MD/C986). According to the χ^2 and I^2 analyses, heterogeneity was observed between the 2 groups ($\chi^2 = 27.04$, $P < .001$, $I^2 = 70\%$; Fig. S6A, http://links.lww.com/MD/C986). Therefore, the random-effects method was used to analyze the data. This revealed that compared to propofol alone, the combined use of propofol and etomidate causes few side effects on injection pain in patients undergoing gastroscopy. Compared to etomidate alone, the combined use of propofol and
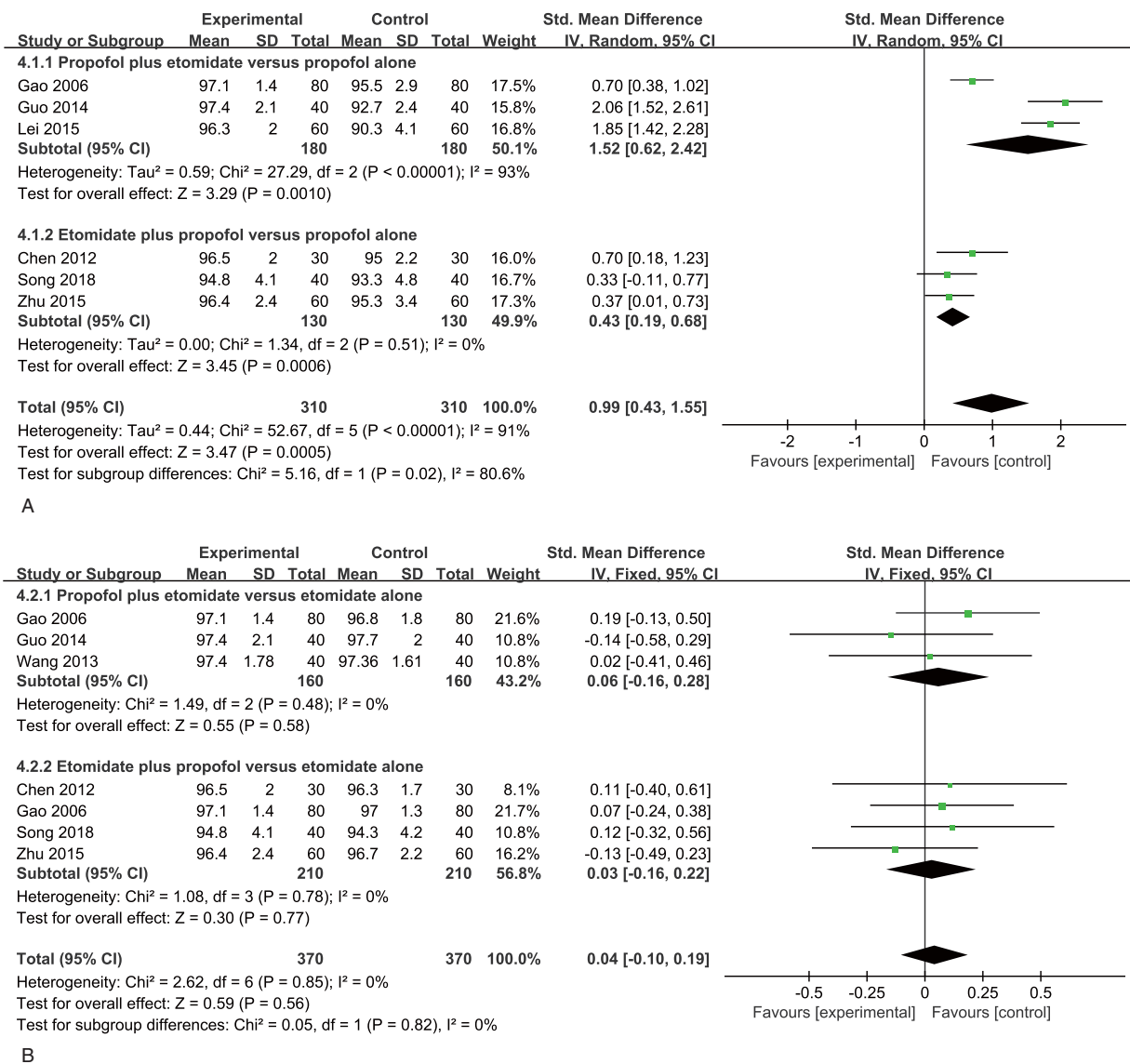
Figure 5. Meta-analysis of SPO_2 (%). (A) SPO_2 after the patients received co-administration of propofol and etomidate vs propofol alone, random-effect model; (B) SPO_2 after the patients received co-administration of propofol and etomidate vs etomidate alone, fixed-effect model.

etomidate showed no significant difference in injection pain (OR = 1.40, 95% CI = 0.92–2.13; P = .11; Fig. S6B, http://links.lww.com/MD/C986). This revealed that compared with etomidate alone, the combined use of propofol and etomidate might not causes side effects on injection pain in patients undergoing gastroscopy.

4. Discussion

This systematic review and meta-analysis systematically and quantitatively evaluates the safety and efficiency of the combined use of propofol and etomidate vs propofol or etomidate alone.

Our meta-analysis demonstrated that compared to propofol alone, co-administration of propofol and etomidate might increase the recovery time of patients undergoing gastroscopy. However, patients treated with etomidate alone had a similar recovery time as those who received propofol and etomidate. Without regard to the influence of recovery time, the combined

use of propofol and etomidate produce safer and more comfortable sedation in patients during gastroscopy.

Propofol is a profound cardiovascular depressant with the side effect of hypotension, which may lead to serious results.[27] On the other hand, propofol for sedation might cause other potential adverse events, such as apnea and desaturation.[4,45,46] High dosage or rapid delivery of propofol can decrease respiratory frequency and tidal volume,[47] which might ultimately cause anoxia. These side effects caused by propofol are closely related to the dose and injection speed.[14] In our study, the combined use of propofol and etomidate improved hemodynamic stability and caused minimal respiratory depression in patients undergoing gastroscopy compared to those treated with propofol alone. This could be due to the fact that the combined use of propofol and etomidate reduced the total dosage of propofol, and the etomidate added to reach the sedation depth. Etomidate has a slight effect on circulation compared to that of propofol. This result demonstrates that etomidate has unique characteristics,
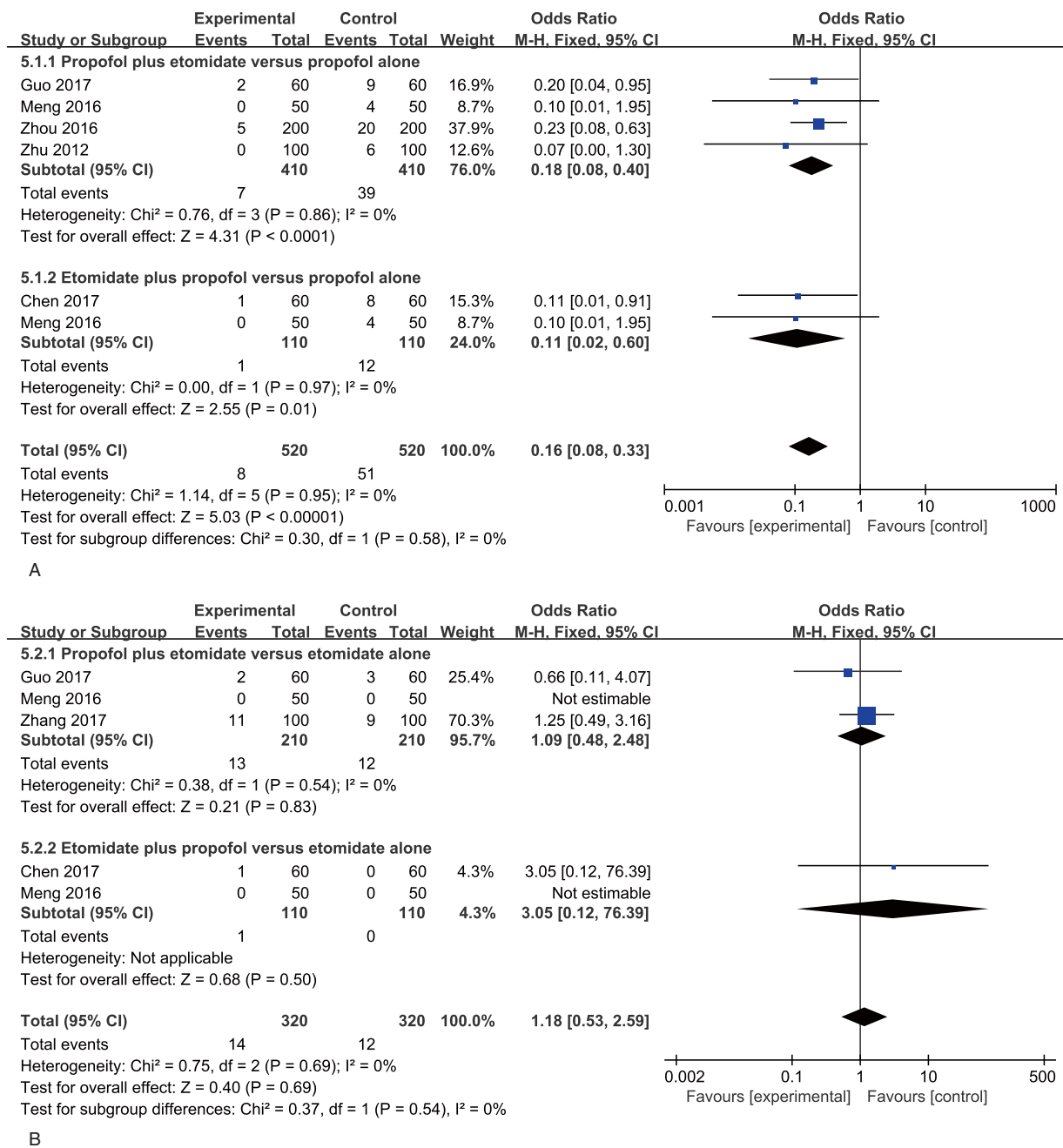
Figure 6. Meta-analysis of apnea or hypoxemia. (A) Co-administration of propofol and etomidate vs propofol alone, fixed-effect model; (B) co-administration of propofol and etomidate vs etomidate alone, fixed-effect model.

which allow it to be used in combination with propofol for anesthesia in patients undergoing gastroscopy.

After operation, the patients treated with etomidate had adverse reactions, such as muscular tremor,[25] nausea, and vomiting.[26] Almost 50% to 80% of patients treated with etomidate possibly developed muscular tremor,[25] which can lead to other adverse reactions, such as postoperative myalgia, and increase in serum potassium levels.[48] In particular, muscular tremors can significantly increase the risk of nausea and vomiting and intragastric pressure.[27] The risk of muscular tremors is related to etomidate dose,[49] and our meta-analysis showed that etomidate combined with propofol can significantly

decrease the risk of muscular tremors. Pretreatment with neuromuscular blocking agent, dexmedetomidine, opioids, low-dose ketamine, midazolam, dezocine, gabapentin and magnesium sulfate could prevent etomidate-related myoclonus, these drugs are associated with side effects such as delayed recovery, excessive sedation, and respiratory inhibition.[38] On the other hand, pretreatment with etomidate plus propofol could inhibit the myoclonus induced by etomidate, as well as had few effects on respiration and circulation in patients, and was safer and more effective than etomidate or propofol alone.

Furthermore, it is important to note that subgroup analysis is supportive of the main research question, that is, whether class

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.1.1 Propofol plus etomidate versus propofol alone						
Guo 2014	1	40	0	40	3.0%	3.08 [0.12, 77.80]
Guo 2017	3	60	1	60	6.0%	3.11 [0.31, 30.73]
Liu 2017	42	218	0	73	3.8%	35.40 [2.15, 582.85]
Meng 2016	2	50	1	50	6.1%	2.04 [0.18, 23.27]
Xu 2015	7	100	5	100	29.4%	1.43 [0.44, 4.67]
Zhou 2016	5	200	2	200	12.3%	2.54 [0.49, 13.24]
Zhu 2012	0	100	2	100	15.7%	0.20 [0.01, 4.14]
Subtotal (95% CI)		**768**		**623**	**76.4%**	**3.29 [1.72, 6.33]**
Total events	60		11			
Heterogeneity: Chi² = 8.21, df = 6 (P = 0.22); I² = 27%						
Test for overall effect: Z = 3.58 (P = 0.0003)						
6.1.2 Etomidate plus propofol versus propofol alone						
Chen 2012	3	30	1	30	5.7%	3.22 [0.32, 32.89]
Chen 2017	0	60	0	60		Not estimable
Meng 2016	3	50	1	50	5.9%	3.13 [0.31, 31.14]
Song 2018	0	40	0	40		Not estimable
Zhu 2015	3	60	2	60	12.0%	1.53 [0.25, 9.48]
Subtotal (95% CI)		**240**		**240**	**23.6%**	**2.34 [0.70, 7.77]**
Total events	9		4			
Heterogeneity: Chi² = 0.34, df = 2 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.38 (P = 0.17)						
Total (95% CI)		**1008**		**863**	**100.0%**	**3.07 [1.73, 5.44]**
Total events	69		15			
Heterogeneity: Chi² = 8.38, df = 9 (P = 0.50); I² = 0%						
Test for overall effect: Z = 3.84 (P = 0.0001)						
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62), I² = 0%						

Favours [experimental] Favours [control]

A

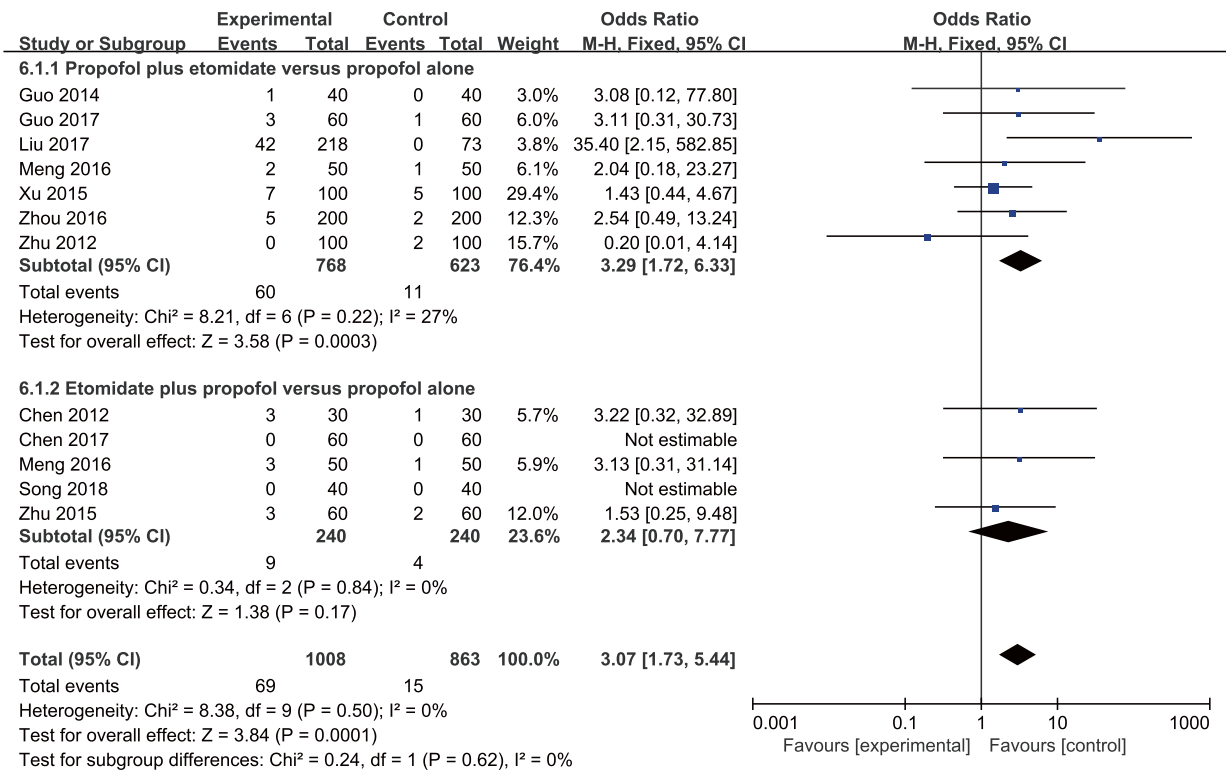| Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
6.2.1 Propofol plus etomidate versus etomidate alone						
Guo 2014	1	40	9	40	4.5%	0.09 [0.01, 0.74]
Guo 2017	3	60	15	60	7.3%	0.16 [0.04, 0.58]
Liu 2017	42	218	35	72	21.8%	0.25 [0.14, 0.45]
Meng 2016	2	50	15	50	7.4%	0.10 [0.02, 0.45]
Wang 2013	8	40	30	40	12.3%	0.08 [0.03, 0.24]
Xu 2015	7	100	22	100	10.5%	0.27 [0.11, 0.66]
Zhang 2017	1	100	13	100	6.6%	0.07 [0.01, 0.53]
Subtotal (95% CI)		**608**		**462**	**70.4%**	**0.17 [0.12, 0.25]**
Total events	64		139			
Heterogeneity: Chi² = 6.18, df = 6 (P = 0.40); I² = 3%						
Test for overall effect: Z = 9.05 (P < 0.00001)						
6.2.2 Etomidate plus propofol versus etomidate alone						
Chen 2012	3	30	17	30	7.9%	0.08 [0.02, 0.34]
Chen 2017	0	60	8	60	4.3%	0.05 [0.00, 0.91]
Meng 2016	3	50	15	50	7.2%	0.15 [0.04, 0.55]
Song 2018	0	40	7	40	3.8%	0.06 [0.00, 1.00]
Zhu 2015	3	60	13	60	6.3%	0.19 [0.05, 0.71]
Subtotal (95% CI)		**240**		**240**	**29.6%**	**0.11 [0.06, 0.24]**
Total events	9		60			
Heterogeneity: Chi² = 1.45, df = 4 (P = 0.84); I² = 0%						
Test for overall effect: Z = 5.90 (P < 0.00001)						
Total (95% CI)		**848**		**702**	**100.0%**	**0.15 [0.11, 0.22]**
Total events	73		199			
Heterogeneity: Chi² = 8.66, df = 11 (P = 0.65); I² = 0%						
Test for overall effect: Z = 10.86 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.33); I² = 0%						

Favours [experimental] Favours [control]

B

Figure 7. Meta-analysis of the myoclonus. (A) Co-administration of propofol and etomidate vs propofol alone, fixed-effect model; (B) co-administration of propofol and etomidate vs etomidate alone, fixed-effect model.

safety and efficiency of different injection sequences between propofol and etomidate are detectable. They should not be regarded as 'independent' investigations and their results should not be overemphasized.

As of now, only one meta-analysis on the comparison of etomidate and propofol anesthesia in patients undergoing gastrointestinal endoscopy has been published.[50] In the meta-analysis, 6 studies from 2009 to 2016 were enrolled. This meta-analysis did not investigate the safety and efficacy of co-administration of propofol and etomidate in patients undergoing gastroscopy. Consequently, to our knowledge, ours is the first meta-analysis to assess the safety and efficacy of co-administration of propofol and etomidate vs etomidate or propofol alone in patients undergoing gastroscopy.

The present study has several limitations. First, the study designed to assess the safety and efficacy of co-administration of propofol and etomidate in patients undergoing gastroscopy was based on data from previous prospective studies, which might cause bias induced by incomplete details, such as the drug dose used, dosing interval, dosage form, duration time for metformin treatment, and other adjunctive therapy. Second, our analysis was based on 15 RCTs and 2 of them had a relatively small sample size (n < 100), and all of included studies were conduct in China. The type of sedative agent used for gastroscopy varies among regional groups according to each domestic healthcare policy and trends. There was significant heterogeneity among the reviewed studies and the risk of introducing potentially significant heterogeneity is imminent. Furthermore, the publication bias in favor of the combined use of propofol and etomidate may account for this heterogeneity after the sensitivity analysis. Different methods and co-administration dosages of etomidate and propofol were included and may have some influence on the pooling results. In addition, variables including age, sex, underlying disease, and nutritional status of patients were also the potential bias-inducing factors. Some unpublished article and missing data might lead to a bias in the pooled effect. Last but not least, a further study with more focus on whether combined use of propofol and etomidate is safe and effective compared with other alternatives anesthetic agent, for example, benzodiazepines and to what extent anesthetic agent for sedation during gastroscopy. Well-conducted RCTs are urgently needed to evaluate the safety and efficacy of the combined use of propofol and etomidate of different age, ethnicity and other variants of patients for sedation during gastroscopy.

5. Conclusions

To our knowledge, this is the first meta-analysis to investigate the safety and efficacy of the combined use of propofol and etomidate. Although various limitations and trials with low methodological quality exist, our meta-analysis recommend that combined use of propofol and etomidate is related to safer and effective for patient's sedation during gastroscopy vs propofol or etomidate alone. In summary, the data suggest that co-administration of propofol and etomidate might increase recovery time vs propofol alone; however, the recovery time was similar to that associated with etomidate. We believe that combined use of propofol and etomidate can be considered as one of the alternatives for sedation during gastroscopy. The combined use of propofol and etomidate can improve hemodynamic stability and minimal respiratory depression, and decrease the risk of injection pain vs propofol alone, and it can

significantly decrease the risk of muscular tremors, nausea and vomiting, body movement, vs etomidate alone. In conclusion, our meta-analysis gives the evidence and suggests that combined use of propofol and etomidate is safe and effective for sedation during gastroscopy. Further study is required to determine whether combined use of propofol and etomidate is safe and effective compared with other alternatives anesthetic agent and to what extent anesthetic agent for sedation during gastroscopy for different age, ethnicity, and other variants.

Author contributions

Conceptualization: Lingyuan Chen, Xinmei Tan, Haibin Wen.
Data curation: Lingyuan Chen, Xinmei Tan, Haibin Wen.
Formal analysis: Lingyuan Chen.
Investigation: Lingyuan Chen, Xueyan Liang, Haibin Wen, Junsong Jiang.
Methodology: Lingyuan Chen, Xueyan Liang, Xinmei Tan, Haibin Wen, Junsong Jiang.
Project administration: Lingyuan Chen, Xueyan Liang, Xinmei Tan, Junsong Jiang.
Software: Xueyan Liang, Yan Li.
Supervision: Yan Li.
Validation: Junsong Jiang, Yan Li.
Visualization: Xueyan Liang, Yan Li.
Writing – original draft: Lingyuan Chen, Xueyan Liang, Xinmei Tan, Yan Li.
Writing – review & editing: Lingyuan Chen, Xueyan Liang, Yan Li.

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