

# Etomidate versus propofol for sedation in gastrointestinal endoscopy

### A systematic review and meta-analysis of outcomes

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#### Abstract

**Background:** Propofol is increasingly being used for sedation in gastrointestinal endoscopy; however, owing to its side effects, an alternative drug is needed. We aimed to compare the safety, satisfaction, and efficacy outcomes of etomidate versus propofol in patients undergoing gastrointestinal endoscopy, including advanced endoscopic procedures.

**Methods:** We systematically searched Embase, PubMed, Cochrane Central Register of Controlled Trials, CINAHL (via EBSCO), China National Knowledge Infrastructure, and Web of Science (1946–April 2020) databases for randomized controlled trials of gastrointestinal endoscopy (upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy) using etomidate or propofol as sedatives. We pooled odds ratios (ORs) for the safety profile and patient and anesthesiologist satisfaction using mixed-effects conditional logistic models and standardized mean differences for efficiency outcomes using random-effects models.

**Results:** Twenty-four studies involving 3875 patients were included. Compared with propofol, etomidate resulted in significantly reduced apnea (OR: 0.22; 95% confidence interval [CI]: 0.13–0.37; P < .001), hypoxemia (OR: 0.43; 95% CI: 0.35–0.54; P < .001), hypotension (OR: 0.20; 95% CI: 0.11–0.36; P < .001), and bradycardia (OR: 0.52; 95% CI: 0.30–0.91; P = .02) but led to increased myoclonus (OR: 8.54; 95% CI: 5.20–14.01; P < .001) and lowered anesthesiologist satisfaction (OR: 0.60; 95% CI: 0.39–0.91; P = .02).

**Conclusion:** Etomidate may be a good alternative to propofol for gastrointestinal endoscopy, especially advanced endoscopy. Etomidate appears to be safe as an inducer for hemodynamically unstable patients or older adult patients undergoing gastrointestinal endoscopy.

**Abbreviations:** CI = confidence interval, OR = odds ratio, RCT = randomized controlled trial, WMD = weighted mean difference. **Keywords:** anesthesia, endoscopy, hemodynamic, intravenous anesthetic agent, respiratory stability

#### 1. Introduction

Sedation is preferred over anesthesia during gastrointestinal endoscopy to minimize patient discomfort and allow examination in a stable state.<sup>[1–3]</sup> To successfully implement therapeutic endoscopy, the selection of an appropriate sedative is crucial for patient safety, patient and physician satisfaction, and maximum efficacy.

Currently, the most commonly used sedatives are midazolam and propofol. In a 2006 survey in the US, midazolam and propofol were used for endoscopy in approximately 75% and 25% of the patients, respectively.<sup>[4]</sup> In a 2016 South Korean survey, propofol was used for gastroscopy in approximately 54% of cases.<sup>[5]</sup> Propofol has amnesic characteristics, the advantage of a short recovery time due to rapid induction of sedation, and high metabolic clearance but also has side effects such as hypotension, respiratory depression, and injection pain.<sup>[6-9]</sup> Additionally, because of the narrow therapeutic window,

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propofol can induce an unintentional deep sedation state, and there is no antagonist. Especially in high-risk procedures and therapeutic endoscopy requiring a long procedure time, the demand for propofol is inevitably high, causing concerns about dose-dependent side effects.<sup>[10]</sup> Contrarily, etomidate has been used as a relatively stable drug to induce anesthesia in hemodynamically unstable patients and is being considered as an alternative to propofol.

Meta-analyses on the 2 drugs are scarce; most of the studies are from China, and none have included advanced endoscopic procedures. Recently, studies comparing the 2 drugs for diagnostic endoscopy and advanced endoscopic procedures have demonstrated different results. Thus, we conducted a meta-analysis to compare the safety, patient and anesthesiologist satisfaction, and efficacy of propofol and etomidate for optimal sedation in gastrointestinal endoscopy, including advanced endoscopy.

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#### 2. Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.<sup>[11]</sup> The protocol for this systematic review was prospectively registered with PROSPERO (CRD42020184276).

#### 2.1. Literature search and selection

The following databases were systematically searched: Embase, PubMed, the Cochrane Central Register of Controlled Trials, CINAHL (via EBSCO), China National Knowledge Infrastructure, and Web of Science (from 1946 to April 2020). Supplementary data and clinicaltrials.gov for unpublished trials were assessed for potentially eligible studies, including a manual search among conference proceedings between 2001 and 2020.

The keywords used were "colonoscopy" OR "colonoscopies" OR "colonoscopes" OR "endoscopy" OR "diagnostic" OR "procedure" OR "technique" OR "advanced" OR "EUS" OR "ERCP" OR "EMR" OR "ESD" OR "endoscopic submucosal dissection" OR "FNA" OR "endoscopic ultrasound" OR "endoscopic retrograde cholangiopancreatography" OR "endoscopic mucosal resection" OR "fine needle aspiration" OR "endoscopic retrograde cholangiopancreatography" OR "endoscopic mucosal resection" OR "fine needle aspiration" OR "intervention" OR "gastrointestinal" OR "gastroscopy." The results were combined with search terms for the sedatives used ("etomidate" AND "propofol"). Additionally, the reference lists from the retrieved articles were manually searched to identify any missed studies. No language restrictions were applied. For non-English papers, we consulted a professional translator.

Both authors independently reviewed the titles and abstracts of all identified and relevant citations that were aggregated and categorized using EndNote X8 (Thomson Reuters, New York, NY). The inclusion criteria were as follows: prospective randomized controlled trials (RCTs); studies including adults aged  $\geq 18$  years who underwent a scheduled elective outpatient gastrointestinal endoscopy; studies comparing a propofol-based sedative regimen with an etomidate-based regimen; and studies assessing the incidence of sedation-related side effects, satisfaction, or efficacy measures as outcomes of interest. We excluded the following studies: non-RCTs, reviews, nonclinical studies, conference abstracts, and case observations; studies with groups that received etomidate plus propofol or propofol plus etomidate; studies reporting the results of a combination of various endoscopic procedures (upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy); and studies not reporting at least 1 outcome of interest.

#### 2.2. Outcome measures

The primary outcome was the safety profile of etomidate and propofol (hypotension, bradycardia, myoclonus, hypoxemia, and apnea). Secondary outcomes were satisfaction or efficacy (patient satisfaction, anesthesiologist-reported satisfaction, and procedure time) (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/I434).

## 2.3. Data extraction and quality assessment in individual studies

Both authors extracted the following data independently from each study: author names, journal, year of publication, country of origin, study population, sample size, study design, patient characteristics (age, sex), sedative characteristics (sedative regimen, protocol, administrator), and primary and secondary study outcomes (number of adverse events per group, time of measurement, satisfaction). Any disagreements in trial eligibility or data extraction between the 2 authors were resolved via consensus. Data were collected from all studies for the full analysis set.

#### 2.4. Methodological quality appraisal

Both authors independently evaluated the methodological quality of all included trials according to the Cochrane Collaboration's Risk of Bias assessment tool Version 2<sup>[12]</sup> using the following methodological parameters: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of appropriate reported findings, and overall risk of bias (see Figure S1, Supplemental Digital Content, http://links.lww.com/MD/ I437).

#### 2.5. Quality assessment and risk of bias

Both authors performed this analysis independently using the Cochrane risk-of-bias tool. Disagreements were resolved through discussions. We recorded the method used to generate the randomization schedule and conceal treatment allocation; whether blinding was implemented for participants, personnel, and outcome assessment; and whether there was evidence of incomplete outcome data and selective reporting of outcomes.

#### 2.6. Data synthesis and statistical analyses

Data analyses were performed using Review Manager Version 5.3 (RevMan v 5.3, The Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-Analysis 3.3.070 (Biostat, Englewood, NJ).<sup>[13]</sup> We also performed 2 additional sets of sensitivity analyses: meta-analyses of only older patients and meta-analyses excluding studies with older adults and patients with obesity. A weighted random-effects meta-analysis was performed to compare etomidate with propofol.<sup>[14]</sup> The relative risk of each outcome was used as the primary outcome measure. The results were presented as forest plots.  $I^2$  values were used to evaluate the heterogeneity. An  $I^2$  value > 50% was considered significantly heterogeneous. Publication bias was tested using funnel plots, and P < .05 was considered significant (see Figure S2, Supplemental Digital Content, http:// links.lww.com/MD/I438). In this study, ethical approval was not necessary because the included data were based on previously published articles, and no original clinical data were collected or utilized.

#### 3. Results

#### 3.1. Study and patient characteristics

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram for the selection process. The initial search strategy identified 16,163 citations. We excluded 11,423 studies by eliminating duplicates and irrelevant studies. After a full-text review of the remaining 64 reports, we identified 24 studies that met the inclusion criteria.[15-38] The characteristics of the included RCTs are presented in Table 1. These studies were published between 2006 and 2020 and investigated a total of 3875 patients: 1913 received etomidate and 1962 received propofol. Twelve studies involved esophagogastroduodenoscopy (2640 patients), 5 involved colonoscopy (534 patients), and 7 involved advanced endoscopy (701 patients). Of the 7 studies involving advanced endoscopy, 4 included endoscopic retrograde cholangiopancreatography (347 patients), 2 included endoscopic ultrasonography (168 patients), and 1 involved a mixture of advanced endoscopy procedures (186 patients).

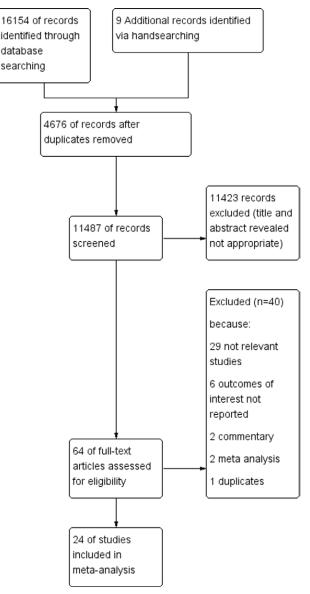


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of assessment procedures.

#### 3.2. Primary outcome (adverse events)

**1.3.2.** *Myoclonus.* Twenty studies (3445 patients) were analyzed. Overall, the etomidate group had a significantly higher proportion of patients with myoclonus than did the propofol group (255/1719 [14.8%] vs 28/1726 [1.6%]; odds ratio [OR]: 8.54; 95% confidence interval [CI]: 5.20–14.01; P < .001; Fig. 2). Subgroup analysis indicated significantly increased myoclonus in the etomidate group compared with the propofol group for each subgroup (upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy) (Fig. 2).

**2.3.2.** Apnea. Eleven studies (1900 patients) were analyzed. Overall, the etomidate group had a significantly lower side effect of apnea than did the propofol group (25/946 [2.64%] vs 82/954 [8.60%]; OR: 0.22; 95% CI: 0.13–0.37; P < .001; Fig. 2). A low level of heterogeneity across the studies was noted ( $I^2 = 0\%$ ; P = .85). Subgroup analysis indicated significantly decreased apnea with the etomidate group compared with the propofol group for all subgroups.

**3.3.2.** *Hypoxemia.* Sixteen studies (3205 patients) were analyzed. Overall, the etomidate group had a significantly lower hypoxemia side effect than did the propofol group (182/1599 [11.38%] vs 335/1606 [20.86%]; OR: 0.45; 95% CI: 0.36–0.55; P < .001; Fig. 2). A low level of heterogeneity across the studies was noted ( $I^2 = 0\%$ ; P = .83). Subgroup analysis indicated that etomidate provided significantly decreased hypoxemia compared with propofol for advanced endoscopy (OR 0.34; 95% CI 0.16–0.69; P = .003) and upper gastrointestinal endoscopy (OR 0.46; 95% CI 0.36–0.58; P < .001), but no difference was found for colonoscopy (OR 0.44; 95% CI 0.15–1.29; P = .14). The  $I^2$  was 0% both for upper gastrointestinal endoscopy and colonoscopy and 9% for advanced endoscopy.

**4.3.2.** *Hypotension.* Twenty studies (3428 patients) were analyzed. Overall, the etomidate group had a significantly lower hypotension side effect than did the propofol group (92/1711 [5.38%] vs 298/1717 (17.36%); OR: 0.20; 95% CI: 0.11–0.36; P < .001; Fig. 2). A high level of heterogeneity across the studies was noted ( $I^2 = 70\%$ ; P < .001). Subgroup analysis indicated significantly decreased hypotension with the etomidate group compared with the propofol group for all subgroups (upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy, (Fig. 2). The  $I^2$  was 82%, 55%, and 0% for upper gastrointestinal endoscopy, colonoscopy, advanced endoscopy, respectively.

**5.3.2.** Bradycardia. Thirteen studies (1521 patients) were analyzed. Overall, the etomidate group had a significantly lower bradycardia side effect than did the propofol group (34/760 [4.47%] vs 70/761 [9.20%]; OR: 0.52; 95% CI: 0.30–0.91; P = .02; Fig. 2). Heterogeneity across the studies was noted ( $I^2 = 23\%$ ; P = .21). However, subgroup analysis indicated no significant difference in bradycardia between the propofol and etomidate groups for each subgroup (upper gastrointestinal endoscopy, colonoscopy, and advanced endoscopy).

#### 3.3. Secondary outcomes (anesthetic performance)

**1.3.3.** Patient satisfaction. Twelve studies (2620 patients) were analyzed. No significant difference was observed in patient satisfaction between the propofol and etomidate groups (OR: 1.071; 95% CI: 0.710–1.614; P = .745; Fig. 3); heterogeneity was observed across the studies ( $I^2 = 43.2\%$ ; P = .062).

**2.3.3.** Anesthesiologist satisfaction. Four studies (1615 patients) were analyzed, all on upper gastrointestinal endoscopy. The etomidate group had a significantly lower physician satisfaction than did the propofol group (688/805 [85.47%] vs 729/810 [90%]; OR: 0.60; 95% CI: 0.39–0.91; P = .02; Fig. 3); heterogeneity was observed across the studies ( $I^2 = 36\%$ ).

**3.3.3. Procedure time.** Seventeen studies (3110 patients) were analyzed. No overall difference in procedure time was observed between propofol and etomidate (weighted mean difference [WMD]: -0.03 min; 95% CI: -0.17-0.12; P = .71; Fig. 3). Heterogeneity across the studies was noted ( $I^2 = 18\%$ ; P = .24). However, subgroup analysis indicated that etomidate had a significantly shorter procedure time than did propofol for advanced endoscopy (WMD: -2.15 min; 95% CI: -4.11--0.19; P = .03; Fig. 3) but a longer procedure time for colonoscopy (WMD: 1.40 min; 95% CI: 0.13-2.68; P = .03; Fig. 3); no difference was found for upper gastrointestinal endoscopy (WMD: 0.00 min; 95% CI: -0.07-0.08; P = .91; Fig. 3).  $I^2$  was 0% for both upper gastrointestinal endoscopy and colonoscopy and 17% for advanced endoscopy.

StudyLumb1Shudycentul1Shen et al,china,2Meng et al,China,2Liu et al,China,12016 <sup>1191</sup> China,22017aChina,22018 <sup>1191</sup> China,5Toklu et al,Turkey,6BanihashemIran, 12015 <sup>1191</sup> China,certal,	number of San centers					Etomidate group	group :			Propofol group	group			
Shen et al, 2015 <sup>[14]</sup> , 2016 <sup>[15]</sup> 2016 <sup>[15]</sup> 2017a <sup>[17]</sup> Xiao 2017 <sup>[16]</sup> 2018 <sup>[16]</sup> 2018 <sup>[16]</sup> 2018 <sup>[16]</sup> 2018 <sup>[16]</sup> 2018 <sup>[16]</sup> 2018 <sup>[16]</sup>		Sample size (E:P)	Operation	Study population	Regimen	Age (yr)	Sex (M/F)	Body weight or BMI	Regimen	Age (yr)	Sex (M/F)	BW or BMI	Outcomes	Protocol
Meng et al, 2016 <sup>[15]</sup> 2016 <sup>[14]</sup> 2017a <sup>[17]</sup> Xiao 2018 <sup>[16]</sup> 2009 <sup>[18]</sup> et al, et al, 2015 <sup>[19]</sup>	China, 1 site	715 ( (355:360)	s	Elderly patients Remifentanil + etomidate	Remifentanil + etomidate	66.3±4.87	200/155	BMI 21.58±3.45	Remifentanil + propofol	66.31±6.9	203/157	BMI 21.86 ± 3.4	a, b, c, d, e, f, g	نن
Liu et al, 2017a rin Xiao 2018 <sup>[16]</sup> 2018 <sup>[16]</sup> 2009 <sup>[18]</sup> et al, et al, 2015 <sup>[19]</sup>	a, 1 site 100	0 (50:50) (	copy Gastrointesti- nal endos-	copy China, 1 site 100 (50:50) Gastrointesti- Elderly patients nal endos-	Fentanyl + etomidate	69.7 (65–80)	25/25	BW 62.4 (52–82)	Fentanyl + propofol	68.4 (65–78)	24/26	BW 60.7 (50-84)	a, d, e, f, g, ľ	<ul> <li>4-6mg</li> <li>P: 0.40.6 μg/kg remitentanil, propofol at 1-2 mg/kg followed by 20-40 mg</li> <li>a, d, e, f, g, h E: 1.0 μg/kg fentanyl, etomidate at 0.15-0.2 mg/kg followed by 0.4 mg/xg/sg</li> </ul>
Xiao 2018 <sup>[16]</sup> Toklu et al, 2009 <sup>[18]</sup> Banihashem et al, 2015 <sup>[19]</sup>	China, 1 site 14	5 (72:73) (	ucupy 14 5 (72:73) Gastrointesti- nal endos- copy	Adult patients (aged 18–80 yr)	Fentanyl + etomidate	51.1±14.2	38/34	BW 67.2±13.9	Fentanyl + propofol	<b>48.4</b> ±10.8	34/39	BW 66.6±14.3	d, f	<ul> <li>P. 1.0 µg/kg fentanyl, propofol at 1.5–</li> <li>P. 1.0 µg/kg fentanyl, propofol at 1.5–</li> <li>2.0 mg/kg, 4.0 mg/kg/h maintenance dose of propofol</li> <li>E: 0.8 mg/kg fentanyl, etomidate induction at 0.3 mg/kg, maintenance infusion of 0.06 mg/kg</li> <li>P. 0.8 mg/kg fentanyl propofol at</li> </ul>
Toklu et al, 2009 <sup>(18)</sup> Banihashem et al, 2015 <sup>(19)</sup>	China, 1 site	300 ( (150:150)	Gastrointesti- nal endos- copy	Overweight or obese patients	Remifentanil <sup>2</sup> + etomidate	Remifentanil 44.54±10.02 101/49 + etomidate	101/49	BMI 28.53±2.21	Remifentanil + propofol	Remifentanil 43.67±9.13 + propofol	103/47	BMI 28.75±2.48	a, b, c, d, e, f, g	
Banihashem et al, 2015 <sup>[19]</sup>	Turkey, 1 site 60	60 (30:30)	Colonoscopy	Adult patients (aged 18–65 yr)	Remifentanil + etomidate	48±11 (28–65)	12/18	BW 72±12 (51-95)	Remifentanil + propofol	51 ± 11 (21−64)	13/17	BW 68 ± 11 (48−87)	c, d, e, g, h	نه نن نه
	Iran, 1 site 90	) (43:47)	90 (43:47) Colonoscopy	Adult patients (aged 18–55 yr)	Fentanyl + etomidate	36.6±9.7	23/20	NA	Fentanyl + propofol	$36.6 \pm 11.4$	23/24	NA	С, Ө	<ul> <li>at 0.5 mg/kg jollowed by 0.25 mg/kg</li> <li>E: 1 µg/kg fentanyl, etomidate at 0.1 mg/kg (15 µg/kg/min)</li> <li>P: 1 µg/kg fentanyl, propofol at 0.5 mg/</li> </ul>
7 Lee et al, South 2019 <sup>[20]</sup> 1	South Korea, 1 site (	200 (1 00:1 00)	Colonoscopy	Colonoscopy Adult patients	Etomidate + 5 midazolam	58.17 ±16.28	54/46	BMI 23.14 ±3.23	Propofol + midazolam	57.14±14.5	50/50	BMI 8 23.83 ± 3.52	a, c, d, f, g, ľ	a, c, d, f, g, h E: 0.05 mg/kg midazolam, etomidate at 0.1 mg/kg midazolam, etomidate at P: 0.05 mg/kg midazolam, propolo at 2.1 mg/kg midazolam, propolo at 2
8 Lee et al, South 2018 <sup>[21]</sup> 1	South Korea, 12 <sup>,</sup> 1 site	4 (62:62)	Colonoscopy	124 (62:62) Colonoscopy Elderly patients	Etomidate + midazolam	$71.37 \pm 5.20$	41/21	BMI 23.32±3.02	Propofol + midazolam	$71.26 \pm 4.53$	37/25	BMI 24.84 ± 2.97	a, c, d, f, g	0.5 mg/kg tollowed by 0.25 mg/kg E: 0.035 mg/kg midazolam, etomidate at 0.07 mg/kg followed by 0.035 mg/kg P: 0.035 mg/kg midazolam, propofol at
9 Wu et al, China, 2017 <sup>/221</sup>	China, 1 site 40	40 (20:20)	Endoscopic ultraso- nography	Adult patients	Fentanyl + etomidate	51.3±10.7	11/9	BMI 22.4 $\pm$ 3.5	Fentanyl + propofol	50.7 ± 11.4	8/12	BMI 22.7 ± 3.6	c, d, f, g	0.35 mg/kg followed by 0.175 mg/kg E: 0.5 µg/kg fentanyl, etomidate at 0.3 mg/kg followed by 0.8–1.0 mg/ kg/h

3		Country and					Etomidate group	group			Propofol group	group			
Sr. DO	Study		Sample size (E:P)	Operation	Study population	Regimen	Age (yr)	Sex (M/F)	Body weight or BMI	Regimen	Age (yr)	Sex (M/F)	BW or BMI	Outcomes	Protocol
10	Kim et al, 2017 <sup>[23]</sup>	South Korea, 1 site	128 (64:64)	Endoscopic ultraso- nography	Adult patients	Etomidate	54.17±14.47	29/35	BMI 23.42±4.13	Propofol	49.83 ± 16.91	33/31	BMI 23.51 ± 4.31	a, c, d, e, f, g, h	E: etomidate at 0.1 mg/kg followed by 0.05 mg/kg P: propofol at 0.5 mg/kg followed by
=	Song et al, 2015 <sup>[24]</sup>	China, 1 site	80 (40:40)	ERCP	Adult patients	Etomidate + midazolam	55.8±10.6	28/12	BW 62.4±11.4	Propofol + midazolam	52.4±11.4	28/12	BW 63.5±11.8	a, c, d, e, f, g, h	E: 0.5 µg/kg fentanyl, etomidate at 0.3 mg/kg followed by 0.8–1.0 mg/ kg/h P: 0.5 µg/kg fentanyl, propofol at
12	Park et al, 2018 <sup>/25]</sup>	South Korea, 127 (64:63) 1 site	127 (64:63)	ERCP	Adult patients	Midazolam + meperidine + etomidate	59.2±17.4	35/29	BMI 24.6±4.2	Midaz- olam + meperidine + proporal	62.7±17.8	25/38	BMI 24.1 ± 4.0	a, c, d, e, f, g, h	<ul> <li>L.O.Ing.kg, 4:U=0.U mg/kg/n</li> <li>E: 1 µg/kg fentanyl, etomidate at 0.3 µg/mL</li> <li>P: 1 µg/kg fentanyl, propofol at 3 µg/mL</li> </ul>
13	Han et al, 2019 <sup>[26]</sup>	South Korea, 186 (92:94) 1 site	186 (92:94)	ERCP, ESD, multiple EMR	Adult patients	Midazolam + fentanyl + etomidate	$60.6 \pm 12.84$	61/31	BMI 23.9±2.98	H fentanyl + propofol	63.9 ± 13.06	62/32	BMI 23.0±3.34	a, c, d, f, g, h	a, c, d, f, g, h E: 0.5 µg/kg remifentanil, etomidate at 0.15–0.3 mg/kg followed by 7.5 mg P: 0.5 µg/kg remifentanil, propofol at 1.0–2.0 mok/kg followed by 15 mg
4	Jain et al, 2020 <sup>i27]</sup>	India, 1 site	60 (30:30)	ERCP	Adult patients (ASA grade IIII, aged 18–70 yr, weight 45–90 kn)	Dexmede- tomidine + midazolam + butorphanol etomidate	NA	NA	NA	Dexmede- tomidine + midazolam + butorpha- nol propofol	NA	NA	NA	a, d	<ul> <li>E: 50 µg fentanyl, etomidate 6–10 mL (0.2%) followed by 1/3–1/4 of the initial dose</li> <li>P: 50 µg fentanyl, propofol 6–10 mL (1%) followed by 1/3–1/4 of the initial dose</li> </ul>
15	15 Wang et al, 2011 <sup>[28]</sup>	China, 1 site	60 (30:30)	Colonoscopy	Adult patients (ASA grade 1-2, aged 18- 70 yr, weight 40-80 km	Fentanyl + etomidate	43±10	14/16	BW 59±12	Fentanyl + propofol	45±9	15/15	BW 62±12	f, g, h	E: 5 mg sufentanil, etomidate at 0.2 mg/ kg P: 5 mg sufentanil, propofol at 0.2 mg/kg
16	Li et al, 2019 <sup>[29]</sup>	China, 1 site	200 (1 00:100)	Gastrointesti- nal endos- copy	Elderly patients (62–73)	Remifentanil + etomidate	63.8±5.2	NA	BW I 77.64±9.04	Remifentanil + propofol	$62.5 \pm 6.8$	NA	BW 78.26 ± 7.91	f, g	<ul> <li>E: 0.5 µg/kg fentanyl, etomidate at 0.2 µg/kg</li> <li>P: 0.5 µg/kg fentanyl, propofol at 1.5</li> </ul>
17	Xu et al, 2015 <sup>[30]</sup>	China, 1 site	200 (100:100)	Gastrointesti- nal endos- copy	Adult patients (ASA grade 1–2, aged 40–60 yr, weight 55–75 kol	Sufentanil + etomidate	$38.2 \pm 5.8$	47/53	BW 66.5±2.6	Sufentanil + propofol	37.9±6.5	63/37	BW 65.3 ± 3.8	c, d, f	E: 2% ildocaine 2 mL, etomidate at 0.2 mg/kg followed by 5–7 mg P: 2% lidocaine 2 mL, propofol at 1.6 mg/kg
100	Guo 2017a <sup>[31]</sup>	China, 1 site	120 (60:60)	120 (60:60) Gastrointesti- nal endos- copy	Adi	Fentanyl + Eetomidate	57.20 ± 12.56	28/32	BW 63.65±6.72	Fentanyl + propofol	55.15 ± 12.73	26/34	BW 61.87±6.43	d, e, g, h	E: 0.1 µg/kg sufentanil, etomidate 50 mL/h (0.2%) P: 0.1 µg/kg sufentanil, propofol 50 mL/h (1%)
															(Continued)

Table 1

		Country and	_				Etomidate group	group			Propofol group	group			
Sr. Do.	Study	number of centers	Sample size (E:P)	e Operation	Study population	Regimen	Age (yr)	Sex (M/F)	Body weight or BMI	Regimen	Age (yr)	Sex (M/F)	BW or BMI	Outcomes	Protocol
19	Guo et al, 2014 <sup>i32]</sup>	China, 1 site	80 (40:40)	80 (40:40) Gastrointesti- nal endos- copy	Elderly patients (ASA grade 1-2, aged 65-77 yr, weight	Fentanyl + etomidate	Ϋ́	NA	M	Fentanyl + propofol	NA	NA	NA	σ	<ul> <li>E: 0.4–0.6 µg/kg remifentanil, etomidate at 0.1–0.15 µg/kg followed by followed by 1/3–1/4 of the initial dose P: 0.4–0.6 µg/kg remifentanil, propofol at 1–2 µg/kg remifentanil, propofol at 2–1.0 of the initial dose</li> </ul>
20	Chen 2017 <sup>[33]</sup>	China, 1 site	120 (60:60)	120 (60:60) Gastrointesti- nal endos- copy	Blde	Sufentanil + E etomidate	56.25 ± 1.89	31/29	BW 61.07 ± 1.61	Sufentanil + propofol	55.15±2.38	30/30	BW 59.69±1.38	c, d, e, g, h	P: E:
21 0	Chun and Zhen 2018 <sup>34</sup>	China, 1 site	200 (100:100)	Gastrointesti- nal endos- copy	Adult patients (ASA grade I–III., agrade 18–65 yr, weight 40–90 kg)	Remifentanil 45.87 ± 12.43 + etomidate	45.87 ± 12.43	66/34	BMI Remifentan 20.39±2.69 + propofol	Remifentanil + propofol	Remifentanii 46.05 ± 11.02 + propofol	68/32	BMI 21.37 ±3.16	a, b, c, d, f, g, h	<ul> <li>E: Dexmedetomidine 1 µg/kg 2 mg midazolam, 1 mg butorphanol etomidate at 0.3 mg/kg followed by 8–10 µg/kg/min</li> <li>P: dexmedetomidine 1 µg/kg, 2 mg midazolam, 1 mg butorphanol propofol at 1.5 mg/kg followed by 100–150 m/kg/min</li> </ul>
22 0	Guo et al, 2017b <sup>[35]</sup>	China, 1 site	400 (200:200)		Gastrointesti- Elderly patients nal endos- (ASA grade copy 1-3, aged 60-80 vr)	Remifentanil + etomidate	67.01 ± 6.92	111/89	BMI F 21.83±3.36	Remifentanil + propofol	Remifentanil 66.83 ± 6.73 + propofol	113/87	BMI 21.62 ± 3.25	a, b, c, d, f, g	шü
23	Liu et al, 2020 <sup>(36)</sup>	China, 1 site	80 (40:40)	ERCP	Adult patients (ASA grade I–III, aged 18–65 yr)	Remifentanil + dexmede- tomidine + etomidate	53±10	22/18	BW 65±13 (BMI 23.3±3.2)	Remifentanil + dexmede- tomidine + propofol	49 ± 11	23/17	BW $68 \pm 10$ (BMI: $24.5 \pm 2.5$ )	c, g, h	<ul> <li>E: 2.0 ng/mL remiferation.</li> <li>E: 2.0 ng/mL remiferation.</li> <li>dexmedetomidine 0.5 µg/kg/h 2min, etomidate at 0.5 µg/mL/</li> <li>P: 2.0 ng/mL remiferation.</li> <li>P: 2.0 ng/mL remiferation.</li> <li>D: norodiate at 2.0 nu/ml.</li> </ul>
24	Liu et al, 2017b <sup>l37]</sup>	China, 1 site	60 (30:30)	Gastrointesti- nal endos- copy	60 (30:30) Gastrointesti- Elderly patients nal endos- (ASA grade copy 1-2, aged 60 yr)	Fentanyl + etomidate	70.1 ± 8.2	20/10	BW 69.8 ±14.3	Fentanyl + propofol	68.7±5.7	18/12	BW 71.5±18.1 c, d, e, g, h	c, d, e, g, h	ы́ i

Table 1

Medicine

Etomidate Propofol Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl	B Etomidate Propolel Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 85% Cl M-H, Random, 95% Cl
T.2.1 EGO         Chen 2017         0         60         12         60         2.8%         0.03 (00.0, 0.69)         Chen 2017           Chun 2018         2         100         26         100         5.6%         0.05 (00.1, 0.25)         0.28 (00.0, 0.44)           Gua 2017a         4         60         12         60         6.1%         0.28 (00.0, 0.44)           Gua 2017b         6         200         4         200         6.1%         1.52 (04.2, 5.45)           Li 2019         1         100         2.10         3.6%         0.49 (04.6, 5.55)           Liu 2017b         1         30         12         3         4.0%         0.05 (001.0.43)           Hung 2016         6         50         4.4         50         0.3%         0.02 (001.0.06)		8.1.1 EGO         Chen 2017         0         60         7         60         3.4%         0.06 [0.00, 1.06]           Chun 2018         3         100         11         100         12.1%         0.25 [0.07, 0.03]           Gua 2017         3         60         4         60         9.6%         0.74 [0.16, 3.34]           Liu 2017b         1         30         6         30         5.5%         0.14 [0.02, 1.23]           Meng 2016         6         5         5         12.2%         12.3 [3.5, 4.32]           Subtotal (95% (0)         300         30         4.4%         0.38 [0.15, 1.06]
$\label{eq:main_stars} \begin{array}{ccccc} Min 2018 & 2 & 64 & 19 & 64 & 55\% & 0.08 [0.02 & 0.34] \\ Shen 2015 & 10 & 355 & 7 & 360 & 6.9\% & 1.48 [0.55 & 3.88] \\ Xiao 2018 & 9 & 150 & 42 & 150 & 7.5\% & 0.15 [0.08 & 0.35] \\ Subtal (195\% (-) & 1199 & 1174 & 54.5\% & 0.17 [0.08, 0.46] \\ Total events & 41 & 10 \\ Herrogrameht, Tau 2 & 01, Chri + 49 & Xid + 9 (P < 0.00001); I' = 82\% \\ Test for overall effect Z = 3.48 (P = 0.0005) \\ \end{array}$	———— ●	Heterogeneity: Taur 2 0.51: Cb <sup>+</sup> = 6.89, df = 4 (P = 0.14); F = 42% Test for overall effect: 2 = 1.85 (P = 0.06) 8.1.2 Colonescopy Les JM 2019 3 100 1 100 5.1% 3.06 [0.31, 29.95] Tokk 2009 0 30 10 30 3.3% 0.03 [0.00, 0.86] Wang 2011 2 30 3 30 7.1% 0.64 [0.10, 4.15] Subtotal (9% C0) 166 165 (% 0.46 [0.46, 4.16]
Z.2 Cohomoscopy         Visual         Visual <t< td=""><td>++ ++ ++</td><td>Total events         5         14           Heterogenety: Tuu* 3.07. Chi* = 6.4, df = 2 (P = 0.04); P = 60%, Test for overall effect. Z = 0.63 (P = 0.53)           8.1.3 Advanced endoscopy           Hum S3 2019         1         92         3         94         5.1%, 0.03 (0.03, 3.26)           Kim MG 2017         10         64         12         64         18.4%, 0.80 (0.32, 2.02)         •           Liu 2020         2         40         3         0.73%, 0.73%,         0.50 (0.10, 4.1)         •</td></t<>	++ ++ ++	Total events         5         14           Heterogenety: Tuu* 3.07. Chi* = 6.4, df = 2 (P = 0.04); P = 60%, Test for overall effect. Z = 0.63 (P = 0.53)           8.1.3 Advanced endoscopy           Hum S3 2019         1         92         3         94         5.1%, 0.03 (0.03, 3.26)           Kim MG 2017         10         64         12         64         18.4%, 0.80 (0.32, 2.02)         •           Liu 2020         2         40         3         0.73%, 0.73%,         0.50 (0.10, 4.1)         •
Test for overall effect: Z = 3.07 (P = 0.002)           7.2.3 Advanced endoscopy           Han SJ 2019         9 92         4 94         2.7%         0.11 [0.01, 2.05]           Kim MG 2017         0 64         3 64         2.6%         0.14 [0.01, 2.69]           Li 2020         0 40         6 40         2.7%         0.07 [0.00, 1.21]		$\begin{array}{cccccccccccccccccccccccccccccccccccc$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	•	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$
Total (95% CI)         1711         1717 100.0%         0.20 [0.11, 0.36]           Total events         52         288         208	02 0.1 1 10 500 Favours [etomidate] Favours [propofol]	
Etomidate Propofol Odds Ratio Study or Subgroup Events Total Weight M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl	D Eternidate Propofol Odds Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl M-H, Random, 95% Cl
13.2.1 EGO         13.2.1 EGO           Chm 2017         8         60         0         2.6%         19.59 [1.10, 347.61]           Chm 2018         9         40         0         100         2.6%         20.87 [1.20, 353.63]           Guo 2014         9         40         0         40         2.6%         20.87 [1.20, 354.53]           Guo 2017a         15         60         1         60         4.6%         19.67 [2.20, 154.47]           Guo 2017b         9         200         2.00         7.0%         4.66 [1.00, 21.87]           Liu 2017a         35         72         0         72         2.7%         139.16 [3.63, 233.16]           Shen 2015         15         30         1         30         4.4%         21.00 [2.6%, 166.45]           Shen 2015         15         35         1         50         4.6%         2.100 [2.6%, 166.45]           Xizo15         22         100         150         4.5%         2.52 [1.54.45]         3.34 [1.38, 2.75.73]           Subcotal (49% Ct)         121         123         120         5.36 [1.4], (4.80)         3.34 [1.48.45]         3.34 [1.48.45]           Subcotal (49% Ct)         1217         1223         44.45		6.3.1 EGD           Chun 2016         19         100         33         100         10.8%         0.48 [0.25, 0.91]           Li 2019         12         200         43         200         15.9%         0.52 [0.34, 1.11]           Li 2019         12         25         200         77%         0.53 [0.24, 1.11]           Mong 2016         0         55         4         50         0.5%         0.10 [0.01, 1.85]           Silen 2016         55         4         50         0.5%         0.10 [0.01, 1.85]         •           Xua 2016         61         150         28 5%         0.53 [0.30, 0.00]         •           Xua 2016         61         150         29 %         0.58 [0.22, 0.58]         •           Xua 2016         61         150         20 %         0.58 [0.23, 0.58]         •           Xua 2016         61         150         20 %         0.58 [0.23, 0.58]         •           Xua 2016         61         150         20 %         0.58 [0.23, 0.58]         •           Xua 2016         61         1127         21 133         854%         0.46 [0.36, 0.56]         •           Heiterscoperty Taru <sup>*</sup> 5.65 (d = 7 / 0 = 0.55); t = 0%
Test for overall effect: Z = 7.89 (P < 0.0001) <b>13.22 Colonoscopy</b> Leo JM 2018 10 62 1 30 4.5% 11.73 [145, 94.71] Leo JM 2019 12 100 4 100 9.9% 3.22 [102, 10.52] Toku 2009 20 30 0 30 2.6% 11.91 (91.65, 12.46, 86.65)] Total events 42 192 17.0% 11.91 [154, 86.65] Total events 42 50 (20.76) = 6.06, df = 2 (P = 0.05); F = 67%, Test for overall effect 2 = 24.5 (P = 0.01)		6.3.2 Colonescopy         Lee, MJ 2018       2       62       5       62       16%,       0.38 [0.07, 2.04]         Lee, JM 2019       2       100       4       100       16%,       0.48 [0.06, 2.74]         Wang 2011       1       30       2       30       0.8%,       0.48 [0.06, 2.74]         Jobitotal (\$6%, 01)       192       192       39%,       0.44 [0.15, 1.28]         Total events       5       5       16% (0.6, 2.74]         Heterogeneity, Taur 2000, Chil+ 0.05, dif = 2 (P = 0.98); P = 0%       16% (0.16, 1.28)         Test for overall effect; 2 = 148 (P, 0.14)       0.14)         6.3.3 Advanced endoscopy       4
13.2.3.Advanced endoscopy         Han S3.2019         11         92         0         94         2.7%         28.67 [1.55,459.61]           Kmin A22019         2         30         0         2.3%         5.35 [0.25,116.31]           Kmin A2017         22         84         8         64         12.8%         3.67 [1.49, 9.04]           Park CH 2018         4         64         2         63         0.0%         2.03 [3.61, 12.7, 10.9]           Wu 2017         7         40         0         40         2.1%         3.06 [10, 27.70.0]           Subtola1(5% Cr)         310         311         2.8.4%         4.22 [2.08, 8.57]         Total events         4.22 [2.08, 8.57]		Hen SJ 2019         1         92         2         94         0.8%         0.51 [0.05, 5.67]           Kim MG 2017         4         64         20         43         55%         0.15 [0.05, 0.64]           Park CH 2018         10         64         16         35%         0.15 [0.05, 0.64]           Storg 32 (51         0         64         0.64         55%         0.54 [0.21, 131]           Storg 32 (51         0         0         0         4%         0.64 [0.21, 131]           Storg 32 (51         0         0         0.4%         0.64 [0.21, 131]           Storg 32 (51         0         0         4%         0.64 [0.21, 131]           Storg 32 (51         0         0         4%         0.44 [0.24, 131]           Storg 32 (51         0         0.4%         0.44 [0.24, 131]         0.64 [0.24]           Store 32 (51         0         0.4%         0.44 [0.24]         0.64 [0.24]         0.64 [0.24]           Store 32 (51         0         0.4%         0.44 [0.24]         0.34 [0.16, 0.69]         0.64 [0.24]           Total events         10         37         0         0.34 [0.16, 0.69]         0.64 [0.24]           Teator coveral effect 2 = 2.46 [0, 0.0003)
$\label{eq:constraints} \begin{array}{c} \text{total reveal} \\ \text{Hetrogeneity} \; \text{Tatu'} = 0.00, \; \text{Ch}^{1} + 4.03, \; \text{ef} = 5 \; (P = 0.54); \; \text{F} = 0\%; \\ \text{Test for overall effect $2 = 3.9(P < 0.0001)$} \\ \hline \\ \text{Test for overall effect $2 = 3.9(P < 0.0001)$} \\ \hline \\ \text{Test for overall effect $2 = 5.8(P < 0.00001)$} \\ \hline \\ \text{Test for overall effect $2 = 6.8(P < 0.00001)$} \\ \hline \\ \hline \\ \text{Test for overall effect $2 = 6.8(P < 0.00001)$} \\ \hline \\ \hline \\ \hline \\ \hline \\ \end{tabular}$	011 0.1 1 10 1000 Favours [cropoto]	Total (35% Cl)         1599         1606 100.0%         0.45 [0.36, 0.69]         ↓           Total events         Tare to rough the constraint of the
	Odds Ratio	
Etomidate         Propofol         Odds Ratio           Study or Subgroup         Events         Total         Weight         M-H, Random, 95% CI           5.2.1 EGD         Chen 2017         0         60         8         60         11.5%         0.05 [0.00, 0.91]	M-H, Random, 95% Cl	
Guo 2017a         3         60         9         60         11.7%         0.30 (0.8.0.16)           Lig2017b         0         30         8         0.11.4%         0.44 (0.0.0.79)         -           Mong 2016         7         50         21         50         24.6%         0.22 (0.61.0.6)         Not estimative           Shan 2015         0         150         0         360         Not estimative           Shabbal 195% (0.7)         705         710         56.2%         0.317 (0.68.0.36)           Total events         1         46         70.5%         1.17 (0.68.0.36)           Total events         1         48.2 (P < 0.00001)	•••	
$ \begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$		
5.2.3 Advanced endoscopy		

Figure 2. Forest plot of randomized controlled trials on the safety profile of etomidate and propofol. (A) Hypotension. (B) Bradycardia. (C) Myoclonus. (D) Hypoxemia. (E) Apnea. CI = confidence interval.

#### 4. Discussion

Total (95% CI)

946 
 Total (95% CI)
 946
 954
 100.0%
 0

 Total events
 25
 82
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Our meta-analysis found no significant overall difference in procedure time or patient satisfaction between etomidate and propofol. However, compared with propofol, etomidate resulted

954 100.0% 0.22 [0.13, 0.37]

0.001

0.1 Favours (

> in significantly reduced apnea or hypoxemia, hypotension, and bradycardia but increased myoclonus.

> Based on the analysis of endoscopy type, no/low heterogeneity was found for procedure time, apnea, and hypoxemia in

Group	Study		Statisti	cs for ea	ach study	<u> </u>		Odds	ratio and	95% C
		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value				
Advanced	Han SJ 2019	0.764	0.453	1.287	-1.011	0.312			-∎∔	1
Advanced	Kim MG 2017	1.740	0.925	3.273	1.717	0.086			⊢∎−	·
Advanced	Park CH 2018	0.492	0.087	2.786	-0.802	0.423				
Advanced	Song 2015	1.000	0.452	2.214	0.000	1.000			-+	
Advanced	Karis h 2020	0.423	0.112	1.596	-1.270	0.204			•	
Advanced		0.935	0.589	1.486	-0.284	0.777			•	
Colono	Lee JM 2018	6.536	0.763	55.988	1.713	0.087			+	╼┼
Colono	Lee JM 2019	1.812	0.682	4.811	1.193	0.233			_+∎-	-
Colono		2.374	0.851	6.619	1.652	0.098				
EGD	Meng 2016	0.102	0.005	1.952	-1.515	0.130	k—			
EGD	Xiao 2018	0.331	0.013	8.193	-0.675	0.500	—		•	
EGD	Guo 2017b	0.497	0.045	5.531	-0.568	0.570		_	-	-
EGD	Chun 2018	3.996	1.080	14.790	2.075	0.038				∎┼
EGD		0.715	0.120	4.278	-0.367	0.713				-
Overall		1.071	0.710	1.614	0.326	0.745			•	
							0.01	0.1	1	10

0.1 1 10 100 Favours [propofol] Favours [etomidate]

#### В

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Chun 2018	53	100	58	100	31.6%	0.82 [0.47, 1.43]	
Guo 2017b	174	200	188	200	23.5%	0.43 [0.21, 0.87]	
Shen 2015	329	355	339	360	29.5%	0.78 [0.43, 1.42]	
Xiao 2018	132	150	144	150	15.5%	0.31 [0.12, 0.79]	
Total (95% CI)		805		810	100.0%	0.60 [0.39, 0.91]	•
Total events	688		729				
Heterogeneity: Tau <sup>z</sup> =	= 0.07; Chi	<sup>z</sup> = 4.70	, df = 3 (F	9 = 0.20	); I <sup>z</sup> = 369	%	
Test for overall effect	Z = 2.39	(P = 0.0	2)			0.01	0.1 1 10 100 Favours [propofol] Favours [etomidate]

#### С

		omidate			opofol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
4.2.1 EGD									
Chen 2017	5.2	0.16	60	5.17	0.31	60	37.5%	0.03 [-0.06, 0.12]	•
Chun 2018	4.74	1.55	100	4.64	1.49	100	9.2%	0.10 [-0.32, 0.52]	t
Guo 2017b	4.77	1.6	200	4.85	1.73	200	13.5%	-0.08 [-0.41, 0.25]	1
Liu 2017b	20.1	10.8	30	21.8	9.5	30	0.1%	-1.70 [-6.85, 3.45]	
Shen 2015	4.74	1.71	355	4.86	1.83	360	18.1%	-0.12 [-0.38, 0.14]	1
Xiao 2018	4.8	2.01	150	4.87	1.73	150	9.1%	-0.07 [-0.49, 0.35]	1
Xu 2015	6.5	1.5	100	6.6	1.3	100	10.5%	-0.10 [-0.49, 0.29]	†
Subtotal (95% CI)			995			1000	98.1%	0.00 [-0.07, 0.08]	
Heterogeneity: Tau <sup>z</sup>	= 0.00; 0	Chi <sup>z</sup> = 2	2.48, df	= 6 (P	= 0.87)	; I <sup>z</sup> = 0	%		
Test for overall effect	t: Z = 0.1	12 (P =	0.91)						
4.2.2 Colonoscopy									
Baniheshem 2015	11.43	4.85	43	9.91	2.17	47	0.8%	1.52 [-0.06, 3.10]	<u> </u>
Lee JM 2018	29.73	12.23	62	29.46	16.04	62	0.1%	0.27 [-4.75, 5.29]	
Lee JM 2019	28.61	11.39	100	27.71	13.88	100	0.2%	0.90 [-2.62, 4.42]	<del></del>
Tokllu 2009	20.76	7.22	30	18.93	5.72	30	0.2%	1.83 [-1.47, 5.13]	+
Subtotal (95% CI)			235			239	1.3%	1.40 [0.13, 2.68]	◆
Heterogeneity: Tauz	= 0.00; (	Chi <sup>z</sup> = 0	).36, df	= 3 (P	= 0.95)	z  = 0	%		
Test for overall effect	t: Z = 2.	16 (P =	0.03)						
4.2.3 Advanced end	loscopy	/							
Han SJ 2019	24.2	15.8	92	28.5	15.38	94	0.1%	-4.30 [-8.78, 0.18]	
	12.91	9.32	64	15.56	10.29	64	0.2%	-2.65 [-6.05, 0.75]	
Kim MG 2017						40	0.1%	0 00 1 5 00 5 401	
	21.4	14.4	40	21.2	9.1	40	0.1%	0.20 [-5.08, 5.48]	
Liu 2020	21.4 16.8	14.4 8.7	40 64	21.2 21.7	9.1 13.3	40 63	0.1%	-4.90 [-8.82, -0.98]	
Liu 2020 Park CH 2018									
Kim MG 2017 Liu 2020 Park CH 2018 Song JC 2015 Wu 2017	16.8	8.7	64	21.7	13.3	63	0.1%	-4.90 [-8.82, -0.98]	
Liu 2020 Park CH 2018 Song JC 2015 Wu 2017	16.8 20.9	8.7 8.4	64 40	21.7 20.4	13.3 9.2	63 40	0.1% 0.1%	-4.90 [-8.82, -0.98] 0.50 [-3.36, 4.36]	
Liu 2020 Park CH 2018 Song JC 2015 Wu 2017 Subtotal (95% CI)	16.8 20.9 45.2	8.7 8.4 11.3	64 40 20 <b>320</b>	21.7 20.4 44.5	13.3 9.2 12.4	63 40 20 <b>321</b>	0.1% 0.1% 0.0% <b>0.7%</b>	-4.90 [-8.82, -0.98] 0.50 [-3.36, 4.36] 0.70 [-6.65, 8.05]	
Liu 2020 Park CH 2018 Song JC 2015	16.8 20.9 45.2 = 1.01; 0	8.7 8.4 11.3 Chi <sup>z</sup> = 6	64 40 20 <b>320</b> 5.01, df	21.7 20.4 44.5	13.3 9.2 12.4	63 40 20 <b>321</b>	0.1% 0.1% 0.0% <b>0.7%</b>	-4.90 [-8.82, -0.98] 0.50 [-3.36, 4.36] 0.70 [-6.65, 8.05]	
Liu 2020 Park CH 2018 Song JC 2015 Wu 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> Test for overall effect	16.8 20.9 45.2 = 1.01; 0	8.7 8.4 11.3 Chi <sup>z</sup> = 6	64 40 20 <b>320</b> 5.01, df	21.7 20.4 44.5	13.3 9.2 12.4	63 40 20 <b>321</b> ; I <sup>z</sup> = 1	0.1% 0.1% 0.0% <b>0.7%</b> 7%	-4.90 [*8.82, -0.98] 0.50 [-3.36, 4.36] 0.70 [-6.65, 8.05] -2.15 [-4.11, -0.19]	 ◆
Liu 2020 Park CH 2018 Song JC 2015 Wu 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> Test for overall effec Total (95% CI)	16.8 20.9 45.2 = 1.01; 0 :t: Z = 2.1	8.7 8.4 11.3 Chi <sup>z</sup> = 6 15 (P =	64 40 20 <b>320</b> 5.01, df 0.03) <b>1550</b>	21.7 20.4 44.5 T = 5 (P	13.3 9.2 12.4 = 0.31)	63 40 20 <b>321</b> ; I <sup>z</sup> = 1	0.1% 0.1% 0.0% <b>0.7%</b> 7%	-4.90 [-8.82, -0.98] 0.50 [-3.36, 4.36] 0.70 [-6.65, 8.05]	• •
Liu 2020 Park CH 2018 Song JC 2015 Wu 2017 <b>Subtotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> Test for overall effec	16.8 20.9 45.2 = 1.01; ( :t: Z = 2.1 = 0.01; (	8.7 8.4 11.3 Chi <sup>z</sup> = 6 15 (P = Chi <sup>z</sup> = 1	64 40 20 <b>320</b> 5.01, df 0.03) <b>1550</b> 19.47, d	21.7 20.4 44.5 T = 5 (P	13.3 9.2 12.4 = 0.31)	63 40 20 <b>321</b> ; I <sup>z</sup> = 1	0.1% 0.1% 0.0% <b>0.7%</b> 7%	-4.90 [*8.82, -0.98] 0.50 [-3.36, 4.36] 0.70 [-6.65, 8.05] -2.15 [-4.11, -0.19]	-10 -5 0 5 10 Favours [etomidate] Favours [propofol]

Figure 3. Forest plot of satisfaction or efficacy of etomidate and propofol. (A) Patient-reported satisfaction. (B) Anesthesiologist-reported satisfaction. (C) Procedure time. Cl = confidence interval.

all types of endoscopies (esophagogastroduodenoscopy, colonoscopy, and advanced endoscopy); no/low heterogeneity was found for myoclonus and bradycardia only in advanced endoscopy. Importantly, the etomidate group showed safer results than the propofol group for hypotension and apnea in all subgroup analyses of esophagogastroduodenoscopy, colonoscopy, and advanced endoscopy. In esophagogastroduodenoscopy and advanced endoscopy, similar results were found for hypoxemia. In colonoscopy, procedure time increased in the etomidate group. However, the etomidate group showed a decrease in procedure time in advanced endoscopy, with etomidate being safer than propofol for sedation and comparable in efficacy.

To date, only 1 meta-analysis has analyzed 6 studies between 2009 and 2016 comparing etomidate and propofol.<sup>[39]</sup> However, all but 1 study had a relatively small sample size (<100), and both gastroscopy and colonoscopy were analyzed together. The majority of the studies were conducted in China; moreover, inaccessible/unpublished articles and missing data can bias the pooled effect. Therefore, we additionally manually searched extensive databases, including CINAHL and China National Knowledge Infrastructure, through exhaustive and contemporary searches for all possible RCTs. We believe ours is the first meta-analysis to analyze the efficacy and safety of etomidate and propofol by endoscopy type, including advanced endoscopy. Our results were mostly consistent with those of previous meta-analyses (patient satisfaction, apnea, hypoxemia, and myoclonus) but did show a few differing results (hypotension). The different types of endoscopies showed high heterogeneity, except advanced endoscopy, which showed no heterogeneity. In contrast to a previous meta-analysis,<sup>[39]</sup> we found that etomidate caused hypotension less frequently than propofol. This is consistent with other reports.<sup>[6,40-42]</sup>

Because etomidate also had safer results than propofol for apnea, hypoxemia, hypotension, and bradycardia, it is considered safe as an inducer in hemodynamically unstable patients and may be considered an alternative to propofol.<sup>[43,44]</sup> Propofol is preferred for shorter procedures because it is a better inducer than etomidate with fewer side effects, faster action, and faster recovery.<sup>[45-47]</sup> Therefore, we suggest that etomidate be the sedative of choice for advanced endoscopy with long procedure times; its side effects may be reduced with pretreatment agents or by combining it with other sedatives. The combined use of propofol and etomidate in gastroscopy can be effective<sup>[48]</sup>; the use of combination drugs in advanced endoscopy can be considered, yet further research is needed.

Lee et al reported that although patients receiving etomidate did not show a significant difference in procedure time from those receiving propofol, the patients who received etomidate presented with more frequent body movements during the procedure and had more frequent side effects that interfered with the procedure than did those who received propofol, making the procedure more difficult for the assistant/nurse than for the endoscopist.<sup>[22]</sup> In our meta-analyses, similar results were seen in the colonoscopy subgroup analysis of 4 studies.<sup>[19-22]</sup> Contrastingly, in our meta-analyses, the procedure time for etomidate was decreased in advanced endoscopy. Of the 6 studies analyzed, 5 did not show a significant difference,<sup>[23-25,27,37]</sup> and only 1 study (Park et al) showed a significant decrease in the etomidate group.<sup>[26]</sup> When that was excluded as leave-1-out, there was no significant difference between the 2 groups, and heterogeneity was reduced from 17 to 0%. Thus, further research is required, and an appropriate drug should be selected according to the patient's age and general condition and the American Society of Anesthesiology score.

Our study had limitations. First, we excluded the analysis of etomidate and propofol combinations; combined use can reduce individual quantities of propofol and etomidate, thus reducing the side effects of each drug. Therefore, further research is needed for optimal sedation. Second, no analysis of sedation administrators was conducted; anes-thesiologists administered sedation in 6 studies,<sup>[15-17,20,35,37]</sup> nurses - trained and certified in advanced cardiac life support - administered anesthesia in 5 studies, [21,22,24,26,27] and the remainder were insufficiently reported. Administrators of sedation vary - nurses, endoscopists and physicians, and gastroenterologists - and may have different levels of training. Furthermore, different sedation levels may be exhibited depending on the administration method. Therefore, our results need to be interpreted with caution. Third, although etomidate and propofol were being evaluated, other pretreatment agents may cause various side effects. Fourth, although the meta-analysis largely included healthy adults, elderly (>60 years old) and obese individuals were included. The

majority of the results of our sensitivity analyses, excluding the older adult and obese patients and including only older adult patients, did not show any significant difference compared with our overall results (see Table S2, Supplemental Digital Content, http://links.lww.com/MD/I435 and Table S3, Supplemental Digital Content, http://links.lww.com/MD/ I436). Our meta-analysis demonstrated that etomidate was safer than propofol for sedation and comparable in efficacy, even for the older adult population.

In conclusion, etomidate can be a good alternative to the conventional sedative, propofol, for sedation in gastrointestinal endoscopy, especially advanced endoscopy. Further studies on the efficacy and safety of pretreatment agents and combinations of sedatives are needed.

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#### **Author contributions**

Conceptualization: Ji Taek Hong, Sung-Wook Park. Data curation: Ji Taek Hong, Sung-Wook Park. Formal analysis: Ji Taek Hong, Sung-Wook Park. Investigation: Ji Taek Hong. Methodology: Ji Taek Hong, Sung-Wook Park. Software: Ji Taek Hong. Writing - original draft: Ji Taek Hong.

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#### References

- [1] Abraham NS, Wieczorek P, Huang J, et al. Assessing clinical generalizability in sedation studies of upper GI endoscopy. Gastrointest Endosc. 2004:60:28-33.
- [2] Igea F, Casellas JA, González-Huix F, et al. Sedation for gastrointestinal endoscopy. Endoscopy. 2014;46:720-31.
- Gouda B, Gouda G, Borle A, et al. Safety of non-anesthesia provider admin-[3] istered propofol sedation in non-advanced gastrointestinal endoscopic procedures: a meta-analysis. Saudi J Gastroenterol. 2017;23:133-43.
- [4] Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a nationwide survey. Am J Gastroenterol. 2006;101:967-74.
- [5] Lee CK, Dong SH, Kim ES, et al. Room for quality improvement in endoscopist-directed sedation: results from the first nationwide survey in Korea. Gut Liver. 2016;10:83-94.
- [6] Zhou X, Li BX, Chen LM, et al. Etomidate plus propofol versus propofol alone for sedation during gastroscopy: a randomized prospective clinical trial. Surg Endosc. 2016;30:5108-16.
- Garewal D, Waikar P. Propofol sedation for ERCP procedures: a [7] dilemma? Observations from an anesthesia perspective. Diagn Ther Endosc. 2012;2012:639190.
- [8] McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. Gastrointest Endosc. 2008;67:910-23.
- [9] Nishizawa T, Suzuki H. Propofol for gastrointestinal endoscopy. United European Gastroenterol J. 2018;6:801-5.
- [10] Wehrmann T, Riphaus A. Sedation with propofol for interventional endoscopic procedures: a risk factor analysis. Scand J Gastroenterol. 2008:43:368-74.
- [11] Salameh JP, Bossuyt PM, McGrath TA, et al. Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): explanation, elaboration, and checklist. BMJ. 2020:370:m2632.
- [12] Yang ZR, Sun F, Zhan SY. [Risk on bias assessment: (2) Revised Cochrane risk of bias tool for individually randomized, parallel group trials (RoB2.0)] [in Chinese]. Zhonghua Liu Xing Bing Xue Za Zhi. 2017;38:1285-1291.
- [13] Borenstein M, Hedges L, Higgins J. Comprehensive Meta Analysis. Englewood: Wiley. 2009.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin [14] Trials. 1986;7:177-88.

- [15] Shen XC, Ao X, Cao Y, et al. Etomidate-remifentanil is more suitable for monitored anesthesia care during gastroscopy in older patients than propofol-remifentanil. Med Sci Monit. 2015;21:1–8.
- [16] Meng QT, Cao C, Liu HM, et al. Safety and efficacy of etomidate and propofol anesthesia in elderly patients undergoing gastroscopy: a double-blind randomized clinical study. Exp Ther Med. 2016;12:1515–24.
- [17] Xiao QS, Liao ST, Liu YH, et al. Comparison of etomidate-remifentanil and propofol-remifentanil sedation in overweight or obese patients prior to diagnostic upper gastrointestinal endoscopy. Int J Clin Exp Med. 2018;11:2839–46.
- [18] Liu J, Liu R, Meng C, et al. Propofol decreases etomidate-related myoclonus in gastroscopy. Medicine (Baltimore). 2017;96:e7212.
- [19] Toklu S, Iyilikci L, Gonen C, et al. Comparison of etomidate-remifentanil and propofol-remifentanil sedation in patients scheduled for colonoscopy. Eur J Anaesthesiol. 2009;26:370–6.
- [20] Banihashem N, Alijanpour E, Basirat M, et al. Sedation with etomidate-fentanyl versus propofol-fentanyl in colonoscopies: a prospective randomized study. Caspian J Intern Med. 2015;6:15–9.
- [21] Lee JM, Min G, Keum B, et al. Using etomidate and midazolam for screening colonoscopies results in more stable hemodynamic responses in patients of all ages. Gut Liver. 2019;13:649–57.
- [22] Lee JM, Min G, Lee JM, et al. Efficacy and safety of etomidate-midazolam for screening colonoscopy in the elderly: a prospective double-blinded randomized controlled study. Medicine (Baltimore). 2018;97:e10635.
- [23] Wu CS, Meng B, Ren HZ. Clinical effects of intravenous anesthesia with etomidate plus propofol for subpyloric endoscopic ultrasonography. WCJD. 2017;25:1405–9.
- [24] Kim MG, Park SW, Kim JH, et al. Etomidate versus propofol sedation for complex upper endoscopic procedures: a prospective double-blinded randomized controlled trial. Gastrointest Endosc. 2017;86:452–61.
- [25] Song JC, Lu ZJ, Jiao YF, et al. Etomidate anesthesia during ERCP caused more stable haemodynamic responses compared with propofol: a randomized clinical trial. Int J Med Sci. 2015;12:559–65.
- [26] Park CH, Park SW, Hyun B, et al. Efficacy and safety of etomidate-based sedation compared with propofol-based sedation during ERCP in low-risk patients: a double-blind, randomized, noninferiority trial. Gastrointest Endosc. 2018;87:174–84.
- [27] Han SJ, Lee TH, Yang JK, et al. Etomidate sedation for advanced endoscopic procedures. Dig Dis Sci. 2019;64:144–51.
- [28] Gupta N, Jain K, Jethava D. Comparison of etomidate and propofol for moderate sedation during ERCP: a randomized clinical study. Indian J Clin Anaesth. 2019;6:587–91.
- [29] Wang S, Wan X, Zhang Y. Application of etomidate or propofol given by target controlled infusion in colonoscopy sedation. China J Endosc. 2011;5:016.
- [30] Li XP, Wang SM. Effect of anesthesia with propofol plus remifentanil vs etomidate plus remifentanil on respiratory function and stress in elderly patients with esophageal leukoplakia treated by gastroscopy. WCJD. 2019;27:822–7.
- [31] Xu J, Meng YG. Clinical effect of etomidate and 1% propofol mixture in patients undergoing gastroscopy. Chin Remed Clin. 2015;15:1349–51.

- [32] Guo G. Clinical application effect of etomidate combined with propofol in patients undergoing analgesia gastroscopy. Med J Chin People Health. 2017;29:33–5.
- [33] Guo B, Zhang SB, Xiao YZ, et al. Clinical effect of propofol combined with etomidate in elderly patients undergoing gastroscopy. J Milit Surg South Chin. 2014;16:654–5.
- [34] Chen H, Wang XY. Clinical application effect of etomidate fat emulsion and propofol mixture in elderly patients undergoing analgesia gastroscopy. Med Innov China. 2017;14:108–11.
- [35] Chun T, Zhen Z. Small dose of remifentanil plus propofol-etomidate anesthesia in painless gastroscopy of adult. Mol Imaging. 2018;41:58–62.
- [36] Guo B, Tang W. Comparison the cardiorespiratory system effects of propofol-remifentanil and etomidate-remifentanil sedation in older patients undergoing painless gastroscopy. Chongqing Med. 2017;46:628–31.
- [37] Liu Yu WX, Huaiyu JI, KangLi Z, et al. Comparison of safety and efficacy of propofol and etomidate target-controlled infusion with remifentanil in ERCP. Med Recapitulate. 2020;26:619–23.
- [38] Liu X, Ren H. Effects of etomidate combined with propofol on painless gastrointestinal endoscopy and cognitive function of elderly patients. China Pharm. 2017;28:2028–32.
- [39] Ye L, Xiao X, Zhu L. The comparison of etomidate and propofol anesthesia in patients undergoing gastrointestinal endoscopy: a systematic review and meta-analysis. Surg Laparosc Endosc Percutan Tech. 2017;27:1–7.
- [40] Doenicke AW, Roizen MF, Kugler J, et al. Reducing myoclonus after etomidate. Anesthesiology. 1999;90:113–9.
- [41] Guler A, Satilmis T, Akinci SB, et al. Magnesium sulfate pretreatment reduces myoclonus after etomidate. Anesth Analg. 2005;101:705–9.
- [42] Yelavich PM, Holmes CM. Etomidate: a foreshortened clinical trial. Anaesth Intensive Care. 1980;8:479–83.
- [43] Möller Petrun A, Kamenik M. Bispectral index-guided induction of general anaesthesia in patients undergoing major abdominal surgery using propofol or etomidate: a double-blind, randomized, clinical trial. Br J Anaesth. 2013;110:388–96.
- [44] Bendel S, Ruokonen E, Pölönen P, et al. Propofol causes more hypotension than etomidate in patients with severe aortic stenosis: a double-blind, randomized study comparing propofol and etomidate. Acta Anaesthesiol Scand. 2007;51:284–9.
- [45] Angsuwatcharakon P, Rerknimitr R, Ridtitid W, et al. Cocktail sedation containing propofol versus conventional sedation for ERCP: a prospective, randomized controlled study. BMC Anesthesiol. 2012;12:20.
- [46] Jung M, Hofmann C, Kiesslich R, et al. Improved sedation in diagnostic and therapeutic ERCP: propofol is an alternative to midazolam. Endoscopy. 2000;32:233–8.
- [47] Kongkam P, Rerknimitr R, Punyathavorn S, et al. Propofol infusion versus intermittent meperidine and midazolam injection for conscious sedation in ERCP. J Gastrointestin Liver Dis. 2008;17:291–7.
- [48] Chen L, Liang X, Tan X, et al. Safety and efficacy of combined use of propofol and etomidate for sedation during gastroscopy: systematic review and meta-analysis. Medicine (Baltimore). 2019;98:e15712.