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Short-Acting Sedative Agents During Endoscopic Retrograde Cholangiopancreatography: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

ASA	American Society of Anesthesiologists
BIS	Bi-Spectral index scale
bpm	beats per minute
CI	confidence interval
DK	dexmedetomidine–ketamine
DR	dexmedetomidine–remifentanil
ERCP	endoscopic retrograde cholangiopancreatography
IQR	interquartile range
ITT	intent-to-treat
MAP	mean arterial pressure
ME	midazolam–etomidate
MF	midazolam–fentanyl
MK	midazolam–ketamine
MM	midazolam–meperidine
MP	midazolam–propofol
MPt	midazolam–pethidine
MR	midazolam–remifentanil
PA	propofol–alfentanil
PE	propofol–esketamine
PF	propofol–fentanyl
PK	propofol–ketamine
PM	propofol–meperidine
PR	propofol–remifentanil
RCT	randomized controlled trial
RSS	Ramsey Sedation Scale
SD	standard deviation
SRS	Steward Recovery Score

Context and Policy Issues

Endoscopic retrograde cholangiopancreatography (ERCP) is essential in the diagnosis and treatment of pancreaticobiliary pathologies.[1] The procedure time ranges from 30 to 60 minutes, and it is commonly performed in endoscopy suites away from the operating room.[2] ERCP is a minimally invasive technique and has fewer complications, generally shorter hospitalization times, and lower medical costs compared to traditional surgery, particularly in sick and elderly patients suffering from hepatobiliary tract disorders.[1] The procedure may be performed under general anesthesia to keep patients stable[3] or with moderate to deep levels of sedation and analgesia to minimize patient discomfort during the procedure.[2] However, potential complications involving respiratory and cardiovascular conditions, which may be related to the level of sedation,[4] may occur during the operation. Essential factors to consider concerning the level of sedation for ERCP procedure include patient tolerance, the presence of comorbidities, the endoscopist's comfort and ease of the procedure, staff, equipment, and anesthesia support available in the endoscopy suite.[2] Benzodiazepine, opiates, and propofol in different combinations are commonly administered to provide conscious or deep sedation for patients undergoing ERCP.[5] It has been reported that one-third to one-half of patients undergoing ERCP under conscious sedation experience discomfort and pain.[6] Thus, there is a need for a sedation method or regimen that offers efficacy and has an excellent safety profile regarding sedation-related side effects.

This report aims to identify and summarize evidence on the clinical effectiveness of short-acting sedative agents for conscious sedation during ERCP. An additional objective is to synthesize evidence-based guidelines for moderate procedural sedation during ERCP.

Research Questions

1. What is the clinical effectiveness of short-acting sedative agents during endoscopic retrograde cholangiopancreatography?
2. What are the evidence-based guidelines for moderate procedural sedation during endoscopic retrograde cholangiopancreatography?

Key Findings

Thirteen randomized controlled trials and one retrospective cohort study provided information regarding the clinical effectiveness of short-acting sedative agents during endoscopic retrograde cholangiopancreatography. The studies covered a wide range of short-acting sedatives, including propofol alone, etomidate alone, and remifentanil alone. Others were propofol-based combinations (i.e., propofol–alfentanil, propofol–esketamine, propofol–fentanyl, propofol–ketamine, propofol–meperidine, midazolam–propofol, and propofol–remifentanil), midazolam-based combinations (i.e., midazolam–etomidate, midazolam–fentanyl, midazolam–ketamine, midazolam–meperidine, midazolam–pethidine, and midazolam–remifentanil), and dexmedetomidine-based combinations (dexmedetomidine–ketamine and dexmedetomidine–remifentanil).

Therefore, although 14 studies were included in this report, they were spread over several unique intervention-comparator pairs. In effect, there was a limited quantity of evidence for each comparison. Also, doses of sedative agents used tended to vary from study to study, so that even where drugs appeared to be the same in two or more studies, they usually differed in doses. Other sources of limitations included inadequate determination of sample

sizes to ensure that studies were adequately powered to determine differences in treatment effects between competing groups, the use of unvalidated methods to assess satisfaction with sedation and pain during the ERCP procedure, lack of adequate blinding in some randomized trials, and the use of data from different historical periods in the retrospective cohort study. Although each of the agents investigated in the included studies demonstrated some effectiveness, given the limitations discussed here and elsewhere in the report, a definitive conclusion could not be drawn about the optimal choice of short-acting sedative agents during ERCP due to the qualitative and quantitative limitations of the evidence that was available for this report.

No relevant evidence-based guidelines were identified for moderate procedural sedation during endoscopic retrograde cholangiopancreatography.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources, including Medline via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were endoscopic retrograde cholangiopancreatography and sedation. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between Jan 1, 2015, and Jul 16, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with suspected problems of the biliary or pancreatic ductal systems
Intervention	Endoscopic Retrograde Cholangiopancreatography (ERCP) performed under moderate procedural sedation with short-acting sedative agents (e.g., midazolam or propofol) or analgesics (e.g., fentanyl), alone or in combination with each other
Comparator	Q1: ERCP performed with: -alternative sedative agent(s) or analgesic, alone or in combination with each other - an alternative dose of the same sedative agents or analgesics ERCP under general anesthesia Q2: not applicable
Outcomes	Q1: Clinical effectiveness (e.g., adequate sedation during the procedure, time to recovery, hypotension, hypoxia, respiratory depression, patient satisfaction) and safety (e.g., hypoxemia, agitation, need for additional sedation before the procedure is complete, emergence delirium, nausea, pain, respiratory arrest, cardiac arrest)

	Q2: Recommendations regarding the optimal agent(s) to use for moderate procedural sedation during ERCP
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, nonrandomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1; they were duplicate publications or were published before 2015. A systematic review[7] in which outcomes of interest were presented only in ranked form was not included since rankings can be misleading.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the Downs and Black checklist[8] for randomized and non-randomized studies. Summary scores were not calculated for the included studies; instead, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 340 citations were identified in the literature search. Following the screening of titles and abstracts, 324 citations were excluded, and 16 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, four papers were excluded for various reasons, and 14 publications met the inclusion criteria and were included in this report. These comprised 13 randomized controlled trials (RCTs)[1-3,5,6,9-16] and one retrospective cohort study.[17] Appendix 1 presents the PRISMA[18] flowchart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Thirteen RCTs[1-3,5,6,9-16] and one retrospective cohort study[17] published between 2015 and 2020 were included in this report. One trial[3] used a noninferiority design for assessing the primary outcome. Seven of the trials were double-blind studies,[3,5,10-13,16] one was single-blind with only investigators blinded. In contrast, four had partial blinding, where the patients and some research staff were blinded to the allocation of study groups, but the endoscopist[15] or sedation practitioners[2,6,9] were not blinded. The retrospective cohort study[17] was based on data from patients who had ERCP in 2016 and 2018 at a single hospital.

Country of Origin

Four RCTs were conducted in China,[1,5,6,16] while two were conducted in Iran,[12,13] two in South Korea,[3,11] and one each in Egypt,[10] India,[2] Netherlands,[9] Turkey,[14] and the United Kingdom.[15] The retrospective cohort study[17] was conducted in Turkey.

Patient Population

All the studies[1-3,5,6,9-17] included in this report were conducted in adults (i.e., 18 years or older) who underwent ERCP procedure. In one RCT,[11] eligibility to participate was limited to patients who were over 80 years old. Also, the retrospective cohort study[17] enrolled only patients who were at least 85 years old. According to the authors, inclusion criteria were restricted to patients belonging to the American Society of Anesthesiologists (ASA) Physical Status Classifications Class I to II,[3,11-13] Class I to III,[1,2,9,14-16] Class III to IV,[17] and Class I to IV.[6,10] One study[5] did not report the ASA classification of the participants. The ASA classification system defines patients' medical co-morbidities conditions before anesthesia. It ranks them in a range from ASA I to ASA VI, where ASA I refers to a regular a healthy patient, and ASA VI describes a patient who has been declared brain dead.[19] Patients in the ASA Classes of II, III, IV, and V, are those with mild systemic disease, severe systemic disease, severe systemic disease that is a constant threat to life, and a moribund patient who is not expected to survive without the operation, respectively.[19] Twelve RCTs[1-3,5,6,10-16] and the retrospective cohort study[17] were conducted at single hospital settings, whereas one RCT[9] was conducted in two hospitals.

Interventions and Comparators

Eleven of the studies[2,3,6,9-14,16,17] included in this report evaluated interventions involving propofol-based sedation protocols. The sedation effectiveness of a combination of propofol with fentanyl (PF) was investigated in six RCTs,[2,6,11-14] where it was compared with combinations of midazolam plus fentanyl (MF),[11] propofol plus ketamine (PK),[12,13] dexmedetomidine plus ketamine (DK),[2] propofol plus meperidine (PM),[6] propofol plus remifentanil,[14] or propofol alone.[14] Propofol alone was also an intervention in two other RCTs,[10,16] in which it was compared with a combination of PK,[10] or etomidate alone.[16] Other comparisons involving propofol-based sedation were propofol plus alfentanil (PA) versus propofol plus esketamine (PE) in one RCT,[9] midazolam plus propofol (MP) versus midazolam plus etomidate (ME) in another RCT,[3] and PK versus midazolam plus meperidine (MM) in one retrospective cohort study.[17]

The remaining three studies[1,5,15] compared midazolam-based sedation with other interventions. One RCT,[1] compared a combination of midazolam plus remifentanil (MR) with dexmedetomidine plus remifentanil (DR), one RCT[5] compared MM with remifentanil alone, and one RCT[15] compared midazolam plus pethidine (MPt) with midazolam plus ketamine (MK).

The doses of the individual drugs varied across the studies. Further details are available in Table 2.

Outcomes

Sedation effectiveness or quality was measured directly using Ramsey Sedation Scale (RSS),[1,12-14] or Bi-Spectral index scale (BIS).[10] The RSS is a validated scale used to evaluate the depth of sedation with scores ranging from 1 to 6, where patients with a score of 1 are described as awake, agitated or restless, or both; and those with a score of 6 are asleep or have no response to a glabellar tap or loud auditory stimulus.[1,13] The BIS assesses the depth of anesthesia on a scale of 0 to 100, using a numerical derivative from brain electrical activity. Zero on the scale represents a state of no detectable brain electrical activity, and 100 represents a state of complete wakefulness. Values below 60 correspond to deep sedation.[10] Indirect assessments of sedation effectiveness were performed using surrogates such as the time to achieve sedation,[17] the total dose (in milligrams) of sedation

medication,[1,9,12,14] doses of medication used to restore sedation (sedation rescue),[1,13,17] and pain during the procedure.[1,5,10,11,15] One RCT[15] assessed pain on a 0 to 4 scale, where zero meant no pain and 4 represented very severe pain. Two RCTs[10,11] reported using a visual analogue scale to assess pain without providing any details about the scales. Two RCTs[1,5] and Zhang et al.[5] did not specify how pain assessments were performed.

Other outcomes of interest included time to recovery,[1-3,6,9-11,13,15,17] satisfaction with sedation (as rated by patients,[1,3,5,9-11,13,15,16] and endoscopists[1-3,5,9-11,13] or gastroenterologist[14,16]), overall hemodynamic stability,[12-14] overall cardiovascular adverse events,[1,11] mean arterial pressure (MAP),[1,13,16] hypotension,[2,5,6,9-11,16,17] bradycardia, [2,5,6,9-11,16,17] heart rate,[1,13,16] respiratory rate,[1,5,13] oxygen desaturation,[6,9-11,13,17] respiratory depression,[1,2,5] apnea,[5,12,13,16,17] hypoxia,[11] nausea and/or vomiting,[1,2,5,9,10,13,15,16] hypersalivation,[10] and agitation.[10]

Eight of the ten studies that reported time to recovery findings defined the outcome based on as time to achieve modified Aldrete score ≥ 9.[2,3,6,9,11,13,16,17] The Aldrete scale is a validated tool with five domains to evaluate recovery after anesthesia.[20] Each domain is rated from 0 to 2 points, with higher scores indicating a greater likelihood of recovery without the need for observation. Ratings of 7 and below indicate a need for continuous observation.[20] One study each assessed time to recovery using BIS (as previously defined) score ≥ 90,[10] or Steward Recovery Score (SRS) of 6.[1] The SRS is a scoring system with three domains for recording post-anesthetic recovery, each rated from 0 to 2 for a total score range of 0 of 6. A score of 0 indicates an unresponsive, immobile patient whose airway requires maintenance, and a score of 10 denotes a fully recovered patient.[21]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

All the studies[1-3,5,6,10-17] included in this report stated their objectives clearly and outlined the inclusion and exclusion criteria. Seven of the RCTs had a double-blind design,[3,5,10-13,16] and six were single or partial blind RCTs. Thus, there was a potential risk for bias in the single or partial blind RCTs due to an uneven approach to sedation rescue and other maneuvers, as a result of knowledge of the sedative intervention to which patients were assigned.[1,2,6,9,14,15] One RCT[3] had a noninferiority design with a prespecified margin of 10%, which was appropriately applied in the interpretation of the results. However, the rationale for choosing that margin level was not provided. Investigators in nine RCTs[1-3,6,9,10,12,13,16] conducted sample size calculations beforehand to determine the number of patients that will adequately power the studies to detect relevant differences in effect between the competing treatment study groups. Sample size calculations were not performed in four RCTs[5,11,14,15] and one retrospective cohort study.[17] However, even in the studies that performed sample size calculations, they were based on primary outcomes and not the secondary and other outcomes. Thus, in comparisons where statistically significant differences in treatment effects in secondary outcomes were not observed, it was unclear whether a larger sample size could have resulted in different results.

All the studies listed the relevant characteristic of the study participants in tabular form. The baseline demographic characteristics, procedure time, and indications for ERCP were similar across the treatment groups, without statistically significant differences in eight RCTs.[1-3,6,10-15] In two RCTs,[5,9] some baseline characteristics (age,[5,9] sex,[9] and cardiovascular disease[9]) appeared dissimilar between the treatment groups. However, P-

values were not reported. Therefore, one could not tell whether the differences were statistically significant. Patients in the two treatment groups of the retrospective cohort study[17] underwent the ERCP procedure in two different periods (midazolam-meperidine group in 2016 and propofol-ketamine group in 2018). Thus, there is a potential for significant differences in the delivery of healthcare over time that could bias outcomes. For example, the duration of the procedure differed significantly between the treatment groups.

The interventions and comparator in all the studies[1-3,5,6,10-17] were described in detail, including doses, mode of administration, and co-administered medications. However, in reporting the doses of drugs used for sedation rescue, one RCT[1] provided data about only one out of at least three drugs that were used for that purpose. The omission to include information about the other rescue medications suggested a risk of bias due to selective reporting. The outcomes measures in all the studies[1-3,5,6,10-17] appeared relevant, and they were well-defined. However, for studies that evaluated satisfaction with sedation[1-3,5,6,9-11,13,15,16] and pain during the ERCP procedure,[1,5,10,11,15] it was unclear if the assessment method had been validated for that purpose. All the studies used appropriate statistical methods to analyze the study outcomes, and they reported the main findings well. In eight RCTs, [3,5,10-13,15,16] the analyses were based on the intention-to-treat (ITT) population involving data from all the patients who were randomized in their original group to which they were assigned. However, five RCTs excluded some patients from analysis for various reasons such as, not receiving allocated intervention,[9] not undergoing the ERCP procedure,[9] failure of intubation,[1] duodenal perforation,[1] severe respiratory depression,[1] missing data,[2,6] procedure termination,[2] and a drop in their oxygen saturation levels during the procedure.[14] In four RCTs,[5,10,12,14] the authors did not acknowledge limitations or consider any in the discussion of results and conclusions of their studies.

Authors of 13 of the included studies declared no conflict of interest. In contrast, no statement on potential conflict of interest or sources of funding was provided in one RCT.[10] Other sources of uncertainty included restricting the study population to low-risk patients, [3,9,11-13] enrollment of only patients of particular geographic origin,[6,16] and limiting eligibility to patients over eighty[11] or eighty-five years old.[17] These limitations potentially restricted the generalizability of the findings to other patients. All studies[1-3,5,6,10-17] included in this report were conducted outside of Canada. Thus, the generalizability of the reported outcomes in the Canadian context is unknown.

Summary of Findings

Appendix 4 presents the main study findings and the authors' conclusions.

Clinical Effectiveness of Short-acting Sedative Agents During Endoscopic Retrograde Cholangiopancreatography

Effectiveness of the sedative or sedation quality

Nine RCTs[1,5,9-15] and one retrospective cohort study[17] reported on the comparative sedation effectiveness of various short-acting sedative agents for ERCP.

Ramsey Sedation Scale as a measure of sedation

Lu et al.[1] reported that dexmedetomidine–remifentanil (DK) combination provided a significantly higher depth of sedation than midazolam–remifentanil (MR) combination ($P < 0.05$). Bahrami Gorji et al.[13] determined that the sedation quality of a propofol–ketamine (PK) combination was statistically significantly better than a propofol-fentanyl (PF)

combination at assessments four minutes (P = 0.037) and 15 minutes (P = 0.035) after the start of sedation, but not at other times (0, 2, 6, 8, 10, 20 minutes) of assessment (P > 0.05). However, Akhondzadeh et al.[12] found no significant difference in the quality of sedation between PF and PK combinations (P = 0.68). Similarly, Haytural et al.[14] found no statistically significant difference in the level of sedation between PF versus propofol–remifentanil combination (PR) versus propofol alone (P > 0.0033; by Bonferroni corrections, where P < 0.0033 was the accepted level statistical significant).

Time to Achieve Sedation

In the retrospective cohort study by Ebru and Resul,[17] the mean (standard deviation [SD]) time to achieve the targeted sedation score of RSS ≥ 4 was statistically significantly longer in the MM conventional group than the PK group (5.41 [0.49] minutes versus 3.21 [0.41] minutes, respectively; P < 0.001).

Total doses of sedation agents as a surrogate measure of the quality of sedation

Eberl et al.[9] reported that patients sedated with a Propofol–Esketamine (PE) combination group received significantly less propofol than those sedated with a Propofol–Alfentanil (PA) combination (8.3 mg/kg/hour versus 10.5 mg/kg/hour; P<0.001). Haytural et al.[14] found that the total dose of propofol administered was statistically significantly higher in the propofol alone group than in the PR group (375 mg versus 150 mg; P < 0.05) or the PF (375 mg versus 245 mg; P < 0.001). They also reported that the total propofol dose administered was statistically significantly higher in the PF group than in the PR group (245 mg versus 150 mg; P < 0.05). However, Akhondzadeh et al.[12] found no significant difference in the total dose of propofol used for sedation between the PF and PK groups (P = 0.36).

Doses of Sedation Rescue as Surrogate

Lu et al.[1] reported that six patients (5.6%) sedated with DK and five patients (5.8%) sedated with MR required additional doses of sedative medication to sustain sedation at the desirable level. They found that the additional dosage of midazolam to maintain sedation was statistically significantly higher in the MR group than the DR group (P < 0.001). It is worth noting that the comparison was limited to midazolam. However, according to the authors, drugs used for rescue sedation during the procedure included midazolam, propofol, and remifentanil.[1] Bahrami Gorji et al.[13] found no statistically significant difference between the PF and PK regarding the need for rescue medication to sustain sedation. The mean (SD) doses of propofol used for rescue were 30.95 (47.77) mg with PF versus 41.00 (64.71) mg with PK (P = 0.45). In the retrospective cohort study by Ebru and Resul,[17] the mean (SD) dose of propofol used as the rescue was statistically significantly higher in the group of patients sedated with midazolam–meperidine (MM) combination than those sedated with PK group (12.15 [0.56] mg versus 10.32 [0.62] mg, respectively; P < 0.001)

Pain During Procedure

In the RCT by Lu et al.,[1] two patients (1.9%) sedated with DK reported a painful procedure compared with six patients (6.9%) sedated with MR. The difference was statistically significant (P = 0.001). Zhang et al.[5] reported that five patients (15.2%) in the MM conventional group experienced pain during the procedure versus three patients (9.1%) each in the remifentanil alone or MR groups. The difference was not statistically significant (P > 0.05 in each comparison). Sayed et al.,[10] Han et al.,[11] and Narayanan et al.[15] also found no significant difference between propofol alone versus PK, PF versus midazolam–

fentanyl (MF), and MP versus MK, respectively, regarding pain during the procedure (P > 0.05 in each study). It should be noted that only Narayanan et al.[15] provided details about the measuring scale for pain (0 to 4 scale, where zero = no pain and 4 = very severe pain). Even so, it was unknown if the scale was validated. Sayed et al.[10] and Han et al. [11] reported using a visual analogue scale to assess pain without providing any details about the scales. Lu et al. [1] and Zhang et al. [5] did not specify how pain assessments were performed.

Time to recovery

Ten RCTs[1-3,6,9-11,13,15,16] and one retrospective cohort study[17] reported time to recovery outcomes for various comparisons between short-acting sedative agents.

The RCT by Sayed et al.[10] found that the mean (SD) time to time to recovery was statistically significantly shorter with propofol alone than PK (7.23 [0.92] versus 13.95 [2.19] minutes, respectively; P = 0.00). The RCT by Han et al.[11] reported that the mean (SD) times to recovery were significantly shorter with PF sedation than with MF (14.11 [4.46] versus 17.91 [6.29] minutes, respectively; P < 0.001). In the RCT by Goyal et al.,[2] the mean (SD) time to recovery was statistically significantly shorter in the PF group than the DK group (5 [5] versus 10 [5] minutes, respectively; P < 0.001) Similarly, the retrospective cohort study by Ebru and Resul[17] found that the mean (SD) time to recovery (RSS ≥ 4) was statistically significantly longer in the MM conventional group than the PK group (5.41 [0.49] minutes versus 3.21 [0.41] minutes, respectively; P < 0.001)

However, in three RCTs by Bahrami Gorji et al.,[13] Lu et al.,[1] Park et al.,[3] and Song et al.[16] there was no significant difference in the mean (SD) time to recovery between the PF versus PK, DR versus MR, etomidate alone versus propofol alone (P> 0.05 in all comparisons). Also, three RCTs by Eberl, et al.,[9] Narayanan et al.,[15] and Shin et al.[6] did not find a statistically significant difference in the median (interquartile range [IQR]) time to recovery between PA versus PE, MP versus MK, and Propofol–Meperidine (PM) versus PF combinations, respectively (P> 0.05 in all comparisons).

Satisfaction with sedation

Twelve RCTs reported satisfaction with sedation outcomes as rated by patients[1,3,5,9-11,13,15,16] and endoscopists,[1-3,5,9-11,13] or gastroenterologists[14,16]

Sayed et al.[10] reported that the overall patients' satisfaction with sedation was statistically significantly higher with propofol alone than with PK combination (P =0.008). Similarly, Lu et al. [1] found that patients' satisfaction was significantly higher in the DR group than the MR group (P = 0.001). Zhang et al.[5] also found that the mean (SD) endoscopists' satisfaction score was generally high in all treatment groups; however, significantly higher with remifentanil alone than both MM (96.2 [4.7] versus 93.5 (5.8), respectively; P< 0.05), and RM (96.2 [4.7] versus 94.9 [5.2], respectively; P< 0.05). However, the difference in the endoscopists' satisfaction score between MM versus RM was not statistically significant

In the other studies, patients in each group had high satisfaction ratings with sedation without statistically significant differences between the treatment groups. In the RCT by Eberl et al.,[9] the median (IQR) patients' satisfaction was not statistically significantly different between PA and PE groups (P=0.812), and there was no significant difference between the groups regarding patients' willingness to recommend the sedation regimen (P=0.33). Likewise, the median (IQR) patients' satisfaction scores in the RCTs by Shin et al.[6] and Song et al.[16] were not statistically significantly different between PM versus PF and etomidate alone versus propofol alone, respectively (P≥0.419). In the RCTs by Han et al.,[11]

Bahrami Gorji et al.,[13] Zhang et al.,[5] and Narayanan et al.,[15] there were no statistically significant differences in the mean (SD) scores for patients' satisfaction with sedation between MF versus PF, PF versus PK, remifentanil alone versus MR, and MP versus MK, respectively (P≥0.646). The RCT by Park et al.[3] found no statistically significant difference between the ME versus MP groups regarding the percentage of patients who were satisfied with sedation (93.8% versus 96.8%, respectively; P = 1.000)

Furthermore, in all the RCTs that reported endoscopist satisfaction, the ratings were similarly high across treatment groups in each study and showed no statistically significant differences. Eberl, et al.[9] and Shin et al.[6] found no statistically significant differences in the median (IQR) endoscopist satisfaction scores between PA versus PE and PF versus PM, respectively (P≥0.199). Similarly, Sayed et al.,[10] Park et al.,[3] and Goyal et al.,[2] reported that the percentage endoscopists' satisfaction with sedation was not statistically significantly different between propofol alone versus PK, ME versus MP, and PF versus DK, respectively (P ≥ 0.113). Haytural et al.[14] also reported that the percentage satisfaction with sedation rating of the attending gastroenterologist was not statistically significantly different between PF versus PR (the p-value was not reported). Likewise, Lu et al.,[1] Han et al.,[11] Bahrami Gorji et al.,[13] and Zhang et al.[5] reported that the mean (SD) endoscopists' satisfaction scores were not statistically significantly different between the DR versus MR, MF versus PF, and PK versus PF, respectively (P ≥ 0.317). Also, Song et al.[16] found that the mean (SD) gastroenterologists' satisfaction score was the same for etomidate alone versus propofol alone (P = 1.000).

Overall Hemodynamic Stability Cardiovascular Events

Four RCTs[1,3,11-14,16] reported on overall hemodynamic stability and cardiovascular events during sedation with short-acting sedative agents for ERCP.

Park et al.[3] identified overall respiratory events in 10 patients (15.6%) in the etomidate group versus 16 patients (25.4%) in the propofol group after sedation. The difference was not statistically significant (P = 0.172). Thus, with a rate difference of -9.8% (97.5% confidence interval [CI], –□ to 4.2%), they concluded that etomidate was non-inferior to propofol in terms of overall respiratory events since the upper bound of the CI was within the prespecified noninferiority margin of 10%. They also reported the rate of adverse respiratory events requiring airway intervention was significantly less in the etomidate group than in the propofol group (9.4% versus 22.2%, respectively; P = 0.047). Park et al.[3] also found that the overall incidence of cardiovascular events was 43 (67.2%) in the etomidate group compared with 32 (50.8%) in the propofol group. The difference was not statistically significant (P = 0.060). Likewise, Han et al.[11] did not find a statistically significant difference in the overall cardiopulmonary event during sedation with MF or PF (P = 0.812).

In the RCT by Lu et al.,[1] the mean (SD) of mean arterial pressure (MAP) decreased from 104 (18) mmHg at baseline to 91 (10) mmHg at the end of the operation in the DR group compared with a decrease from 102 (16) mmHg to 99 (13) mmHg for the MR group. The difference between the two groups was statistically significant (P = 0.001). Also, the mean (SD) heart rate values decreased to from 87 (19) beats per minute (bpm) to 84 (14) bpm in the DR group, whereas in the MR group the heart rate increased from 83 (15) bpm at baseline to 98 (14) bpm. The difference between the two groups was statistically significant (P = 0.008).[1] Similarly, Song et al.[16] found that the mean (SD) drop from baseline in MAP during the ERCP procedure was statistically significantly less with etomidate than propofol (-8.4 [7.8]% versus -14.4% [9.4]%, respectively; P = 0.002). However, the mean (SD)

percent change from baseline heart rate was not statistically significantly different between etomidate and propofol (P = 0.874).

The RCTs by Akhondzadeh et al.,[12] Bahrami Gorji et al.,[13] and Haytural et al.[14] found no statistically significant differences between the PF versus PK, PF versus PK, and PF versus PR versus propofol alone, respectively, regarding the overall MAP,[13,14] systolic blood pressure,[12,14] diastolic blood pressure,[12,14] respiratory rate,[13] and heart rate[12,13] during and after the procedure (P > 0.05 in all comparisons).

Hypotension

Seven RCTs[2,5,6,9-11,16] and one retrospective cohort study[17] provided comparative outcomes on hypotension during sedation with various sedative agents.

In the RCT by Goyal et al.,[2] hypotension was identified in eight patients (19%) in the PF group, whereas there was no incident of hypotension among patients in the DK group. The difference was statistically significant (95% CI 0.07 to 0.31; Fisher exact test). Eberl, et al.,[9] Sayed et al.,[10] Han et al.,[11] Zhang et al.,[5] Shin et al.[6] and Song et al.,[16] did not observe a statistically significant difference in the incidence of hypotension between PA versus PE, propofol alone versus PK, PF versus MF, MM versus remifentanil alone versus RM, PF versus PM, and etomidate alone versus propofol alone, respectively (P ≥ 0.10). Similarly, the retrospective cohort study by Ebru and Resul,[17] found no statistically significant difference between the MM and PK groups in the number of patients who had hypotension during the procedure (P = 0.300)

Bradycardia

Seven RCTs[2,5,6,9-11,16] and one retrospective cohort study[17] provided comparative outcomes on bradycardia during sedation with various sedative agents

In the RCT by Goyal et al.,[2] two patients (4.7%) in the PF group had bradycardia, whereas there was no incident of bradycardia among patients in the DK group. The difference was statistically significant (95% CI 0.0 to 0.31; Fisher exact test). Similarly, the retrospective cohort study by Ebru and Resul,[17] the number of patients in whom bradycardia was identified during the procedure was statistically significantly more in the MM group than the PK group (17 [22.7%] versus 2 [2.7%], respectively; P < 0.05). Eberl et al.,[9] Sayed et al.,[10] Han et al.,[11] Zhang et al.,[5] Shin et al.[6] and Song et al.,[16] did not observe a statistically significant difference in the incidence of hypotension between PA versus PE, propofol alone versus PK, PF versus MF, MM versus remifentanil alone versus RM, PF versus PM, and etomidate alone versus propofol alone, respectively (P ≥ 0.08 in all comparisons).

Oxygen desaturation

Six RCTs[1,3,6,9,10,16] and one retrospective cohort study[17] reported comparative findings on oxygen desaturation during sedation with various sedative agents.

In the RCT by Lu et al.,[1] desaturation occurred 19 patients (22%) in the MR group compared with none in the DR group. The difference was statistically significant (P = 0.001). However, in the RCTs by Eberl et al.,[9] Sayed et al.,[10] Park et al.,[3] Shin et al.,[6] and Song et al.,[16] as well as the retrospective cohort study by Ebru and Resul,[17] there was no statistically significant difference in desaturation between PA versus PE, propofol alone versus PK, ME versus PM, PF versus PM, etomidate alone versus propofol alone, and MM versus PK groups, respectively (P ≥ 0.172 in all comparisons).

Respiratory depression

Two RCTs[9,10] reported findings on respiratory depression, during sedation with short-acting sedative agents for ERCP.

Goyal et al. [2] reported that respiratory depression was not identified in any patients sedated with DK compared with five patients (11.9%) who had respiratory depression following sedation with PF. The difference was statistically significant (95% CI, 0.02 to 0.22; Fisher exact test). Similarly, Zhang et al.[5] found that the number of patients who experienced respiratory depression was statistically significantly lower with remifentanil alone than with MM (11 [33%] versus 3 [9.1%]; P< 0.05) or RM group (10 [20.3%] versus 3 [9.1%]; P< 0.05).

Apnea and Hypoxia

Five RCTs[5,11-13,16] and one retrospective cohort study[17] provided outcomes on apnea,[5,12,13,16,17] and hypoxia[11] during sedation with various short-acting sedative agents for ERCP.

Akhondzadeh et al.[12] reported that statistically significantly more patients sedated with PF experienced apnea compared with those who were sedated with PK (31 [63%] versus 16 [32.7%], respectively; P < 0.05). However, Bahrami Gorji et al.,[13] did not observe a statistically significant difference in the number of patients who had apnea following sedation with PF or PK (7 [16.7%] versus 1 [3.3%], respectively; P = 0.128). In the RCT by Zhang et al.,[5] no patients sedated with remifentanil alone experienced apnea. In contrast, apnea was identified in one patient (3.0%) in the MM group and four patients (12.1%) in the RM groups. The difference was statistically significant only when comparing the remifentanil alone with RM groups (P< 0.05). Similarly, the retrospective cohort study by Ebru and Resul[17] found that the number of patients who had apnea during the procedure was statistically significantly more in the MM group than the PK group (22 [29.3%] versus 3 [4.0%], respectively; P < 0.05). There was no incidence of apnea following sedation with either etomidate alone or propofol alone in the RCT by Song et al..[16] The RCT by Han et al.[11] found no statistically significant difference in the number of patients in whom hypoxia occurred while sedated with PF or MF (P = 0.779).

Nausea, Vomiting, or Hypersalivation

Seven RCTs[1,2,5,10,13,15,16] reported on the incidence of nausea or vomiting and hypersalivation[10] following the use of various short-acting sedative agents for ERCP.

In the RCT by Lu et al.,[1] nausea and vomiting occurred in statistically significantly more patients sedated with DR than patients sedated with MR (7 [6.5%] versus 2 [2.3%], respectively; P = 0.001). Zhang et al.[5] reported that nausea or vomiting occurred in two patients (6.1%) sedated with MM compared with seven patients (21.2%) who received remifentanil alone, and nine patients (27.3%) who received RM. The difference was statistically significant only when comparing MM versus RM (P< 0.05). Sayed et al.,[10] Bahrami Gorji et al.,[13] Goyal et al.,[2] Narayanan et al.,[15] Song et al.[16] found no statistically significant difference in the incidence of nausea or vomiting between propofol alone versus PK, PF versus PK, PF versus DK, MP versus MK and etomidate alone versus propofol alone, respectively (P ≥ 0.239 for in all cases). Sayed et al.[10] also reported that the incidence of hypersalivation following sedation was not statistically significantly different between propofol alone versus PK (P = 0.246).

Agitation

In the RCT by Sayed et al.,[10] the number of patients who exhibited agitation after sedation was not statistically significantly different between PK versus propofol alone (P = 0.239).

Evidence-based guidelines for moderate procedural sedation during endoscopic retrograde cholangiopancreatography

No relevant evidence-based guidelines regarding the use of ondansetron for palliative patients were identified; therefore, no summary can be provided.

Limitations

Although 14 studies were included in this report, they were spread over several unique intervention-comparator pairs. In effect, there was a limited quantity of evidence for each comparison. Also, doses of sedative agents used tended to vary from study to study, so that even where drugs appeared to be the same in two or more studies, they usually differed in doses. In that sense, it was challenging to assign effects to drug protocols with no standardized doses. Moreover, there were studies that enrolled unique populations such as only Asians[6,16] or patients over eighty[11] or eighty-five years old,[17] which prevented comparisons across studies. For some outcomes, including but not limited to time to recovery and satisfaction with sedation, the difference in score between groups seemed numerically small yet they were statistically significant in some cases. Thus, in the absence of a defined minimally clinically important difference, the clinical relevance of the differences between the groups were unknown.

Furthermore, all the studies included in this report[1-3,5,6,9-17] were conducted outside Canada. Therefore, the generalizability of the findings to the Canadian context is unclear, given the potential for differences in practice patterns, including differences in drug availability or use in practice, that might impact the interpretation of the results or the resources used to achieve them.

Conclusions and Implications for Decision or Policy Making

Thirteen RCTs[1-3,5,6,9-16] and one retrospective cohort study[17] were identified regarding the clinical effectiveness of short-acting sedative agents during ERCP. No relevant evidence-based guidelines were identified for moderate procedural sedation during ERCP.

There was a total of eight RCT involving sedation with propofol alone or in combination with other drugs such as alfentanil, esketamine, fentanyl, ketamine, midazolam, meperidine, and remifentanil. Apart from a combination of propofol and midazolam (MP), six other midazolam-based sedative agents were investigated in which midazolam was combined with etomidate, fentanyl, ketamine, meperidine, pethidine, or remifentanil. Other drugs that were investigated were dexmedetomidine–ketamine (DK) combination dexmedetomidine–remifentanil (DR) combination, etomidate alone, and remifentanil alone.

In assessing the comparative effectiveness of sedation using propofol as a standalone short-acting sedative for ERCP, evidence from one RCT[10] indicated no significant difference between propofol alone and a propofol–ketamine (PK) combination in terms of pain during the procedure. Based on the total doses of propofol used during ERCP procedures, evidence from one RCT[14] suggested that the effectiveness of propofol alone was significantly less effective compared to propofol–fentanyl (PF) or propofol–remifentanil (PR) combination. Regarding the sedation effectiveness of propofol–alfentanil (PA) and

propofol–esketamine (PE), evidence from one RCT[9] indicated that PE was significantly more effective than PA as a short-acting sedative for ERCP, as assessed by the total dose of propofol used during the procedure for ERCP. Evidence from one RCT[13] suggested that the sedation quality, as measured by RSS, may be significantly better with a PK than with PF at some points (four minutes and 15 minutes) during the ERCP procedure. However, in the same RCT,[13] there was no evidence of a significant difference in sedation effectiveness between PF and PK in terms of additional doses of propofol used to sustain sedation during the procedure. Likewise, evidence from another RCT[12] indicated no significant difference in the quality of sedation between the PF and PK as measured by RSS or the total dose of propofol used for sedation. Evidence from one RCT[11] showed no significant difference between PF versus a midazolam–fentanyl (MF) combination in pain during sedation. Another RCT[3] found no evidence between PF versus PR regarding the effectiveness of sedation using the RSS.[14] For sedation effectiveness in terms of time to achieve RSS sedation, evidence from one retrospective cohort study[17] showed that PK was significantly more effective than a midazolam–meperidine (MM). In that study, the dose of propofol used as the rescue was significantly higher with MM.

Evidence from three RCTs[2,10,11] and one retrospective cohort study[17] showed that the time to recovery was significantly shorter with propofol alone than PK,[10] PF than MF,[11] PF than DK,[2] and PK than MM.[17] Evidence from seven RCTs indicated no significant difference in time to recovery between PF versus PK,[13] DR versus MR,[1] ME versus MP,[3] etomidate alone versus propofol alone,[16] PA versus PE,[9] MPt versus MK,[15] and PF versus PM.[6]

For satisfaction with sedation, evidence from three RCTs[1,10] suggested that patients were significantly more satisfied with propofol alone than PK[10] and with DR than MR.[1] Evidence from one RCT showed that endoscopists were significantly more pleased with sedation with remifentanil alone than MM. For all other comparisons, there was no significant difference in patients' or endoscopists'/gastroenterologists' satisfaction with one sedative agent over the others.

For overall hemodynamic stability and cardiovascular events, evidence from one RCT indicated that ME was not inferior to MP in terms of the overall respiratory events, and adverse respiratory events requiring airway intervention were significantly less with ME than MP. However, there was no evidence that one sedative agent (ME or MP) was associated with significantly lower overall cardiovascular events in patients who underwent ERCP. Evidence from two RCTs indicated that the MAP decreased markedly more during the ERCP procedure with DR than MR, and with etomidate alone than propofol alone. Comparisons of PF versus PK,[12,13] and PF versus PR versus propofol alone did not show evidence of a significant difference between the sedative agents in MAP,[13,14] systolic blood pressure,[12,14] diastolic blood pressure,[12,14] respiratory rate,[13] and heart rate[12,13] during the procedure.

Concerning hypotension, evidence from one RCT[2] indicated that sedation with DK was associated with significantly less hypotension than sedation with PF. In other comparisons six RCTs[5,6,9-11,16] and one retrospective cohort study[17] found no evidence of a significant difference in the incidence of hypotension between PA versus PE,[9] propofol alone versus PK,[10] PF versus MF,[11] MM versus remifentanil alone versus RM,[5] PM versus PF,[6] etomidate alone versus propofol alone,[16] and MM versus PK.[17]

Regarding bradycardia, evidence from one RCT[2] and one retrospective cohort study[17] suggested a significantly higher incidence of bradycardia following sedation with PF than DK[2] or MM than PK.[17] In other comparisons, evidence from six RCTs[5,6,9-11,16] did not

indicate a statistically significant difference in the incidence of hypotension between PA versus PE,[9] propofol alone versus PK,[10] PF versus MF,[11] MM versus remifentanil alone versus RM,[5] MP versus PF,[6] and etomidate alone versus propofol alone[16]

Evidence from one RCT[1] indicated that the incidence of oxygen desaturation was significantly higher following sedation with MR than sedation with DR. In other comparisons, evidence from five RCTs,[3,6,9,10,16] and one retrospective cohort study[17] suggested no significant difference in the incidence of desaturation following sedation with PA versus PE,[9] propofol alone versus PK,[10] ME versus MP,[3] MP versus PF,[6] etomidate alone versus propofol alone[16] and MM versus PK.[17]

Evidence from two RCTs[2,5] indicated that respiratory depression during sedation occurred significantly more frequently with PF than DK[2] and MM than remifentanil alone.[5] Similarly, evidence from two RCT[5,12] and one retrospective cohort study[17] showed that the incidence of apnea was significantly higher with PF than PK,[12] MM than remifentanil alone,[5] and MM than PK.[17] In other comparisons, evidence from four RCTs[5,11,13,16] did not show a significant difference in the incidence of apnea between PF versus MF[11] PF versus PK,[13] MM versus RM,[5] and etomidate alone versus propofol alone.[16]

Two RCTs[5],[1] had evidence suggesting that the incidence of nausea and vomiting was significantly higher sedation with DR than MR,[1] and with RM than MM.[5] In other comparisons, evidence from six RCTs[2,5,10,13,15,16] indicated that the incidence of nausea and vomiting was not significantly different following sedation with propofol alone versus PK,[10] PF versus PK,[13] PF versus DK,[2] MP versus MK,[15] and etomidate alone versus propofol alone.[16] Evidence from one RCT[10] suggested no significant difference between propofol alone versus PK regarding the incidence of hypersalivation or agitation following sedation.

In addition to the limitations discussed under the critical appraisal section, it is essential to note that although 14 studies were included in this report, they were spread over several unique intervention-comparator pairs. In effect, there was a limited quantity of evidence for each comparison. Also, doses of sedative agents used tended to vary from study to study, so that even where drugs appeared to be the same in two or more studies, they usually differed in doses. Therefore, although each of the agents investigated in the included studies demonstrated some effectiveness, a definitive conclusion could not be drawn about the optical agent or agents for short-term sedation during ERCP due to the limitations in the quality and quantity of evidence available for this report. There is a need for more rigorous studies comparing standardized doses of particular short-acting sedative agents in a large population with a wide diversity of patients. The analysis in such a study should consider stratification for essential subgroups such as high-risk and low-risk patients as well as those in different age brackets.

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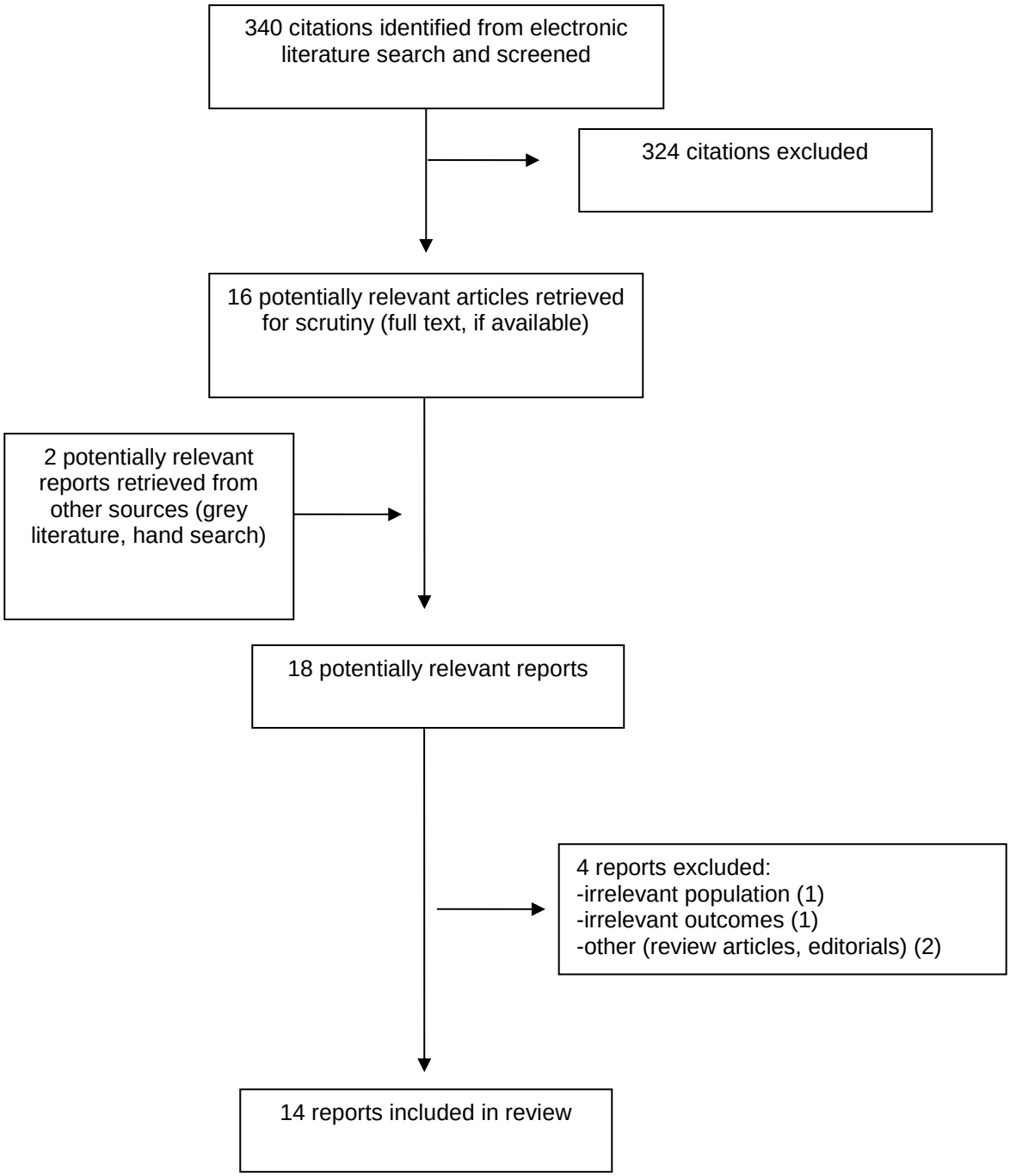
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up

Eberl, et al., 2020[9]
 	
The Netherlands
 	
Funding Source: None
	A multicenter (i.e., conducted in two hospitals), partial-blind randomized, controlled trial.	A total of 166 adult patients (ASA I to III), who were scheduled to undergo elective ERCP were randomized.
		
		The median (IQR) patient age was 58 (43 to 70) years in the propofol-alfentanil (PA) group and 63 (52 to 73) years in the propofol-esketamine (KE) group
			Propofol (1.5 mcg/kg) + Alfentanil (2.0 mcg/kg) (PA group; n=79)
			
			Versus
			
			Propofol (1.5 mcg/kg) + Esketamine (150 mcg/kg) (PE group; n=83)
			
			Sedation was maintained at the desirable level by increasing or decreasing plasma propofol concentration by 0.5 mcg/mL every 3 minutes.
				• Effectiveness of the sedative adjunct (i.e., using total dose of propofol as a surrogate).
				• Time to recovery (based on MAS of 9)
				• Satisfaction with sedation
				  • Hypotension
				  • Bradycardia
				• Oxygen desaturation
				• Vomiting

Sayed et al., 2019[10] **Egypt** **Funding Source:** Not reported	A single-center, double-blind, randomized, controlled trial.	A total of 80 patients, (ASA I to IV), who scheduled to undergo ERCP were randomized. The mean (SD) patient age was 48 (12) years in the propofol group and 45 (13) years in the ketamine + propofol (ketofol) group.	Propofol alone 1.5 mg/kg over 5 minute and followed by 50 to 75 mcg/kg/minute as maintenance dose (n=40) Versus Propofol 8 mg + Ketamine 2 mg (PK group; n=40) All patients also received 25 mcg fentanyl.	• Time to recovery (i.e., to achieve BIS ≥ 90) • Pain during procedure • Satisfaction with sedation • Hypotension • Bradycardia • Oxygen desaturation • Vomiting • Agitation • Hypersalivation
LU et al., 2018[1] **China** **Funding Source:** None	A single-center, partial-blind, randomized, controlled trial	A total of 198 adult patients (ASA I to III), who were scheduled to undergo elective ERCP were randomized. The mean patient age was 60.6 years in the midazolam–remifentanil (MR) group and 60.5 years in the dexmedetomidine–remifentanil (DR) group	Midazolam (0.05 mg/kg) + Remifentanil (1 mcg/kg loading dose) (MR group; n=89) Versus Dexmedetomidine (1 mcg/kg over 10 minutes) + Remifentanil (1 mcg/kg loading dose) (DR group; n=109) All patients also received 0.05 to 0.2 mcg/kg/minute of remifentanil.	• Depth of sedation by RSS • Additional drug uses • Time to recovery (i.e., to achieve SRS 6) • Pain during procedure • Satisfaction for sedation • Mean arterial pressure • Heart rate • Oxygen desaturation • Respiratory depression

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
			Midazolam dose of 0.02 mg/kg was given as necessary, and the infusion rate of remifentanil was increased at the same time to maintain adequate sedation.	• Nausea and/or vomiting
Park et al., 2018[3] **Korea** **Funding Source:** Hallym University Research Fund	A single-center, double-blind, randomized, controlled trial, with noninferiority design. [a]	A total of 127 adult patients (ASA I to II), who were scheduled to undergo elective ERCP were randomized. The mean patient age was 59 years in the midazolam-etomidate (ME) group and 63 years in the midazolam-propofol (MP) group	Midazolam (0.05 mg/kg) + Etomidate (0.05 mg/kg) (ME group; n=63) Versus Midazolam (0.05 mg/kg + Propofol (0.25 mg/kg (MP group; n=64). Repeated doses of 0.05 mg/kg etomidate or 0.25 mg/kg propofol were administered, when necessary, to maintain the target level of sedation, in the respective groups.	• Overall respiratory events • Respiratory events requiring airway intervention • Time to recovery (based on MAS of 9) • Satisfaction for sedation • Oxygen desaturation • Overall cardiovascular adverse events
Han et al., 2017[11] **Korea** **Funding Source:** Soonchunhyang University Research Fund.	A single-center, double-blind, randomized, controlled trial.	A total of 100 patients over 80 years of age (ASA I to II), who required therapeutic ERCP were randomized. The mean (SD) patient age was 83.96 (3.75) years in the propofol–fentanyl (PF) group and 84.18 (4.27) years in the midazolam–fentanyl (MF) group	Propofol (0.5 mg/kg) + Fentanyl (12.5 to 50 mcg) (PF group; n=50) Versus Midazolam (0.05 mg/kg) + Fentanyl (12.5 to 50 mcg) (MF group; n=50) Repeated doses of 0.5 to 1 mg midazolam or 5 to 10 mg propofol were given in their respective groups to achieve and maintain a moderate level of sedation.	• Time to recovery (based on MAS of 9) • Pain during procedure • Satisfaction with sedation Hypotension • Overall cardiovascular adverse events • Hypotension • Bradycardia • Hypoxia
Akhondzadeh et al., 2016[12] **Iran**	A single-center, double-blind, randomized, controlled trial.	A total of 98 adult patients (ASA I to II), who were referred to undergo ERCP were randomized.	Propofol (0.5 mg/kg) + Fentanyl (1 mcg/kg) (PF group; n=49) Versus	• Effectiveness of sedation • Hemodynamic indices • Incidence of apneas

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding Source: Ahvaz Jundishapur University of Medical Sciences and Pain Research Center		The mean (SD) patient age was 42.22 (7.10) years in the propofol-fentanyl (PF) group and 41.18 (5.98) years in the propofol-ketamine (PK) group	Propofol (0.5 mg/kg) + Ketamine (0.5 mg/kg) (PK group; n=49) All patients in in each group received 0.05 mg/kg of intravenous midazolam at the beginning. A bolus dose of propofol 0.5 mg/kg, repeated every 60 seconds, if necessary, was prescribed to maintain adequate sedation.	
Bahrami Gorji et al., 2016[13] **Iran** **Funding Source:** None	A single-center, double-blind, randomized, controlled trial	A total of 72 adult patients (ASA I to II), who were referred for ERCP were randomized. The mean (SD) patient age was 60.50 (15.66) years in the propofol-fentanyl (PF) group and 56.00 (19.75) years in the propofol-ketamine (PK) group	Propofol (0.5 mg/kg loading dose) + Fentanyl (50 to 100 mcg) (PF group; n=42) Versus Propofol (0.5 mg/kg loading dose) + Ketamine (0.5 mcg/kg) (PK group; n=30) All patients in each group received 0.05 to 1 mg/kg of intravenous midazolam before the start of ERCP. Propofol 75 mcg/kg/minute infusion was given to maintain sedation in all patients.	• Sedation quality • Rescue dose of propofol • Time to recovery (based on MAS of 9) • Satisfaction with sedation • Hemodynamic indices ▪ Incidence of apnea ▪ Nausea and/or vomiting
Goyal et al., 2016[2] **India** **Funding Source:** None	A single-center, partial-blind, randomized, controlled trial	A total of 83 adult patients (ASA I to III), who were scheduled for elective ERCP were randomized. The mean (SD) patient age was 59.2 (14.4) years in the propofol-fentanyl (PF) group and 60.4 (13.8) years in the	Propofol (1.0 mg/kg loading dose, followed by 2 to 4 mg/kg/hour infusion) + Fentanyl (1.0 mcg/kg) (PF group; n=42) Versus Dexmedetomidine (0.5 mcg/kg loading dose followed by 0.5	• Time to recovery (based on MAS of 9) • Satisfaction with sedation • Hypotension • Bradycardia Oxygen desaturation • Respiratory depression • Nausea and/or Vomiting

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		dexmedetomidine-ketamine (DK) group	mcg/kg/hour infusion) + Ketamine (1.0 mcg/kg loading dose, followed by 1 to 2 mg/kg/hour infusion) (DK group; n=41) Propofol 0.25 mg/kg was used in group PF and Ketamine 0.25 mg/kg in group DK, in the form of a bolus were used as rescue to maintain sedation.	
Zhang et al., 2016[5] **China** **Funding Source:** Libang Scientific Research Funds of the Chinese Medical Association Anesthesiology Society	A single-center, double-blind, randomized, controlled trial	A total of 99 adult patients who were undergoing diagnostic and therapeutic ERCP were randomized. The ASA classification of the patients was not reported. The mean (SD) patient age was 58.5 (11.9) years in the Midazolam–Meperidine (MM) group, 63.3 (12.1) years in the Remifentanil alone group, and 57.0 (12.4) years in the Remifentanil-Midazolam (RM) group	Midazolam (2.5mg) + Meperidine (2.5 mg). It was followed by intermittent bolus dose of meperidine (12.5 to 50 mg) or midazolam (0.5 to 2.5 mg) to maintain sedation at desired level. (MM group; n=33) Versus Remifentanil alone (0.2 mcg/kg/minute initial dose, followed by 0.15 mcg/kg/minute 5 minutes later) (R group; n=33) Versus Midazolam (0.02 mg/kg) + Remifentanil (0.2 mcg/kg/minute initial dose, followed by 0.15 mcg/kg/minute 5 minutes later (MR group; n=33)	• Pain during procedure • Satisfaction with sedation • Hypotension • Bradycardia • Respiratory depression • Apnea • Nausea and/or Vomiting
Haytural et al., 2015[14] **Turkey** **Funding Source:** None	A single-center, single-blind, randomized, controlled trial	A total of 90 adult patients (ASA I-III), who underwent elective ERCP were randomized. The mean (SD) patient age was 51.6 (12.9) years in the propofol alone group, 52.1 (16.4) years in the propofol-remifentanil (PR)	Propofol (1.5 mg/kg) + Fentanyl (1 mcg/kg) (PF group; n=30) Versus Propofol (1.5 mcg/kg) + Remifentanil (0.5	• Sedation quality • Total dose of propofol • Overall hemodynamic stability • Gastroenterologist satisfaction

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		group, and 50.3 (13.3) years in the propofol-fentanyl (PF) group	mcg/kg/minute) (PR group, n=30) Versus Propofol alone (1.5 mg/kg) (Propofol group; n=30), All the patients were given 1 mg/kg/hour maintenance dose of propofol infusion. All the patients were given 0.5 mg/kg bolus of propofol when necessary, and the patients in the PF group were given 0.01 mg/kg bolus of fentanyl to maintain at the targeted level.	
Narayanan et al., 2015[15] **United Kingdom** **Funding Source:** Multiple sources	A single-center, partial-blind, randomized, controlled trial	A total of 41 adult patients (ASA I-III), scheduled to undergo ERCP were randomized. The median (IQR) patient age was 69 (64 to 75) years in the midazolam–pethidine (MPt) group and 64 (59 to 79) years in the midazolam–ketamine (MK) group	Midazolam (1 to 2 mg) + Pethidine (25 mg) (MPt) conventional group; n=20) Versus Midazolam (1 to 2mg) + Ketamine (12.5 to 25 mg). (MK group; n=21) Further bolus doses (not specified) of midazolam or pethidine in the conventional group or a midazolam and ketamine mixture in the KM group were given to maintain sedation if necessary.	• Time to normal activity • Satisfaction with sedation • Pain during procedure • Nausea and/or Vomiting
Shin et al., 2015[6] **China** **Funding Source:** None	A single-center, partial-blind, randomized, controlled trial	A total of 215 adult patients (ASA I – IV) scheduled for ERCP were randomized. The mean (SD) patient age was 65.3 (13.8) years in the propofol–fentanyl (PF) group and 60.9 (14.6) years in the propofol–meperidine (PM) conventional group.	Propofol infusion (0.4 mg/kg) + Fentanyl (1 mcg/kg initial bolus), followed by propofol infusion at a maintenance rate of 30 mcg/kg/minute (PF group, n=102) Versus	• Time to recovery (based on MAS of 10) • Satisfaction with sedation • Hypotension • Bradycardia • Oxygen desaturation

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
			Propofol infusion (1 mg/kg) + Meperidine (25 mg initial bolus), followed by propofol infusion at a maintenance rate of 60 mcg/kg/minute (PM group, n=100) Additional doses of 10 mg of propofol were given for insufficient sedation in both groups, and pain in the conventional group. Bolus doses of 0.5 mcg/kg of fentanyl were given for pain in the PF group.	
Song et al 2015[16] **China** **Funding Source:** National Natural Science Foundation of China and B. Braun Fund for Anesthesia Scientific Research	A single-center, double-blind, randomized, controlled trial	A total of 80 patients (ASA I – III) undergoing ERCP were randomized. The mean (SD) patient age was 55.8 (10.6) years in the etomidate group and 52.4 (11.4) years in the propofol group.	Etomidate alone (30 mcg/kg/minute, followed by infusion of 8 to 12 mcg/ kg/ minute to maintain sedation (etomidate group, n=40) Versus Propofol alone (0.3 mg/kg/ minute, followed by infusion at a maintenance rate of 0.12 to 0.18 mg//kg/ minute (propofol group, n=40) All patients received intravenous midazolam (2 to 2.5 mg) five minutes before the induction of sedation was started with the study drugs.	• Change in MAP and heart rate • Time to recovery (based on MAS of 9) • Satisfaction with sedation • Hypotension • Bradycardia • Oxygen desaturation • Apnea • Nausea and/or Vomiting
Ebru and Resul, 2019[17] **Turkey** **Funding Source:** None	A retrospective single center cohort study	Data from a total of 150 patients aged 85+ years (ASA III – IV) who underwent ERCP were compared. The mean (SD) patient age was 88.15 (3.11) years in the ketofol group and 87.99 (2.62) years in the MM group	Propofol (0.5 mg/kg) + Ketamine (0.5 mg/kg) both as IV bolus, followed by a titration of a 1:1 mixture of the two drugs to maintain sedation (ketofol group; n=75) Versus Midazolam (2.5 mg) + Meperidine (0.5 mg/kg)	• Time to achieve targeted sedation (RSS ≥4), • Amount of propofol used as a rescue medication • Time to recovery (MAS ≥9) • Bradycardia • Hypotension • Oxygen desaturation

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
			both as IV bolus, followed by repeated doses of 1 mg midazolam as needed to maintain sedation. (MM group; n=75)	• Apnea

ASA = American Society of Anesthesiologists; BIS = Bi-Spectral Index; ERCP = endoscopic retrograde cholangiopancreatography; IQR = interquartile range; IV = intravenous; MAP = mean arterial pressure; MAS = Modified Aldrete Score; mg = milligrams; mcg =micrograms; RSS = Ramsay Sedation Scale; SD = standard deviation; SRS = Steward Recovery Score.

[a] Noninferiority was assessed for only overall respiratory event (the primary endpoint), with a 1-sided a of 2.5%. A noninferiority margin of 10% was assumed. All other comparisons applied tests superiority tests, with the level of statistical significance set at a 2-sided α of 5%.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[8]

Strengths	Limitations
Eberl, et al., 2020[9]	
• A randomized controlled trial with the objective and hypothesis of the study stated clearly • Inclusion and exclusion criteria were stated, and the primary and secondary outcomes were described clearly. • Sample size was calculated for main outcome • Characteristics of patients described • Outcomes were reported clearly with actual probability values. • Statistical tests appeared to be appropriate and results were reported with estimates of variability (e.g., IQR, SD) • The authors declared no conflict of interest and there was no external source of funding.	• The study was partially blinded with patients, researchers, nurses, and endoscopist blinded, but not sedation staff. Therefore, a risk for bias existed due to potential for uneven approach to sedation rescue and other maneuvers. • Despite randomization, some baseline characteristics appeared dissimilar between the treatment groups. For example, patients in the esketamine group appeared to be older with a median (IQR) age of 63 (52 to 73) years compared with 58 (43 to 70) years in the alfentanil group. Also 15% of patients in the esketamine group had cardiovascular disease compared with 6.3% in the alfentanil group. However, the comparison of baseline characteristics did not statistical. Therefore; it was unclear whether the differences were statistically significant, and it was unknown how variation impacted the results. • Patients with ASA PS IV classification were excluded, and according to the authors, the number of ASA PS III patients enrolled was very small (no number specified). Therefore, the study population was mainly made up of low-risk patients. Thus, the generalizability of the findings in the high-risk population that requires ERCP was unknown. • It was unknown if satisfaction with sedation was assessed with a validated the tool. • The analysis was not based on ITT population since four patients (one from the in the propofol-alfentanil group and three from the propofol-esketamine group) were dropped from analysis due for not receiving allocated intervention or undergoing the ERCP procedure. The impact of the missing data on the results is unknown. • The study was conducted in two institution in the Netherlands. Thus, the generalizability of the reported finding in the Canadian context is unknown.
Sayed et al., 2019[10]	
• A double-blind randomized controlled trial with the objective stated clearly • Inclusion and exclusion criteria were stated, and calculations were performed beforehand to determine a sample size that ensured the study was adequately powered for main outcome. • Demographic characteristics, procedure time and indications for ERCP were similar across the treatment groups at baseline without a statistically significant difference. • The intervention and comparator were described well	• It was unknown if the tool used to assess satisfaction with sedation was validated. • The authors did not report limitations or consider such in the discussion and conclusions of their study. • There was no statement on potential conflict of interest or sources of funding. • The study was conducted in a single institution in Egypt. Thus, the generalizability of the reported finding in the Canadian context is unknown.

Strengths	Limitations
• Overall, the outcomes measures were valid and well-defined. • The analysis of results used appropriate statistical methods, and actual probability values were reported for the findings. • Outcome data for the main findings were reported clearly, with estimates of random variability.	
Lu et al., 2018[1]	
• A randomized trial with the objective stated clearly • Inclusion and exclusion criteria were stated, and calculations were performed beforehand to determine a sample size that ensured the study was adequately powered for main outcome. • Demographic characteristics, procedure time and indications for ERCP were similar across the treatment groups at baseline without a statistically significant difference. • The intervention and comparator were described well • Overall, the outcomes measures were valid and described clearly • The analysis of results used appropriate statistical methods, and actual probability values were reported for the findings. • Outcome data for the main findings were reported clearly, with estimates of random variability. • The authors declared no conflict of interest and there was no external source of funding.	• A single-blind study with patients and all investigators were blinded to the group allocation but not the anesthesiologist. • It was unknown if the tool used to assess satisfaction with sedation was validated. • Analysis was not based on ITT population since four patients (three from the dexmedetomidine–remifentanil [DR] group and one from the midazolam–remifentanil (MR) group) were excluded from analysis after randomization for intubation failure duodenal perforation or severe respiratory depression) • According to the authors, additional drugs administered if patient movement occurred during the procedure included midazolam, propofol, and remifentanil. However, the amount of additional drug used was specified only for midazolam, suggesting a risk of bias due to selective reporting. • The study was conducted in a single institution in China. Thus, the generalizability of the reported finding in the Canadian context is unknown.
Park et al., 2018[3]	
• A double-blind randomized controlled trial with the objective stated clearly. • Inclusion and exclusion criteria were stated, and calculations were performed beforehand to determine a sample size that ensured the study was adequately powered for main outcome. • The intervention and comparator were described well • Overall, the outcomes measures were valid and described clearly • The analysis was based ITT population with no missing data. • The analysis of results used appropriate statistical methods, and actual probability values were reported for the findings. • A noninferiority margin was set beforehand and appropriately used in the interpretation of the results. • Outcome data for the main findings were reported clearly, with estimates of random variability. • The authors declared no conflict of interest and the research was funded by a university research fund.	• The study was conducted in a low-risk population and excluded patients with ASA PS III or IV. Thus, the generalizability of the findings in the high-risk population that often requires ERCP was unknown. • Despite randomization, patients with an identified potential confounder (alcohol intake) were twice as many in the etomidate group than the propofol at the baseline (34.4% versus 17.5%; P=0.03). The impact of the dissimilarity of the reported outcome was unknown. • Staff of different qualification administered the sedatives, including endoscopists, nurses who were formerly trained for sedation, and nurses who had not been formerly trained for sedation. Thus, it is unknown whether potential differences in skill between the staff could have influenced the reported outcomes. • The rationale for setting the noninferiority margin at 10% was not provided. • It was unknown if the tool used to assess satisfaction with sedation was validated. • The study was conducted in a single institution in Korea. Thus, the generalizability of the reported finding in the Canadian context is unknown.

Strengths	Limitations
Han et al., 2017[11]	
• A double-blind randomized controlled trial with the objective stated clearly. • Inclusion and exclusion criteria were stated. • Demographic characteristics, procedure time and indications for ERCP were similar across the treatment groups at baseline without a statistically significant difference. • The intervention and comparator were described well • Overall, the outcomes measures were valid and described clearly • The analysis was based ITT population with no missing data. • The analysis of results used appropriate statistical methods, and actual probability values were reported for the findings. • Outcome data for the main findings were reported clearly, with estimates of random variability. • The authors declared no conflict of interest and the research was funded by a university research fund.	• Sample size calculation was not done because there were no direct comparative studies between these protocols in elderly patients. • A single tertiary center in a restricted area of Korea • Although the study was designed as a s double-blind trial, repeat injections of sedation drugs to sustain was not done in a blinded manner. Thus, there is a potential for bias in the survey results. • The study included low-risk patients with ASA PS I–II classification. Thus, the generalizability of the findings in the high-risk population that requires ERCP was unknown. • It was unknown if the tool used to assess satisfaction with sedation was validated. • The study was conducted in a single tertiary center in a restricted area of Korea. Thus, the generalizability of the reported finding in the Canadian context is unknown.
Akhondzadeh et al., 2016[12]	
• A double-blind randomized controlled trial with the objective stated clearly. • Inclusion and exclusion criteria were stated, and calculations were performed beforehand to determine a sample size that ensured the study was adequately powered for main outcome. • Demographic characteristics, procedure time and indications for ERCP were similar across the treatment groups at baseline without a statistically significant difference. • The intervention and comparator were described well • The outcomes measures were valid and described clearly • The analysis was not based ITT population with no missing data. • The analysis of results used appropriate statistical methods, and actual probability values were reported for the findings. • Outcome data for the main findings were reported clearly, with estimates of random variability. • The authors declared no conflict of interest and the research was funded by a university research fund.	• The generalizability of the finding in patients older than 65 years is unknown since the study excluded patients who were more than 65 years. • The study included low-risk patients with ASA PS I–II classification. Thus, the generalizability of the findings in the high-risk population that requires ERCP was unknown. • The authors did not acknowledge limitations or consider any in the discussion and conclusions of their study. • The study was conducted in a single center in Iran. Thus, the generalizability of the reported finding in the Canadian context is unknown.
Bahrami Gorji et al., 2016[13]	
• A single-blind randomized controlled trial with the objective stated clearly. • Inclusion and exclusion criteria were stated, and calculations were performed beforehand to determine a sample size that ensured the study was adequately powered. for main outcome.	• The study included low-risk patients with ASA PS I–II classification. Thus, the generalizability of the findings in the high-risk population that requires ERCP was unknown. • Single-center study in Iran. All ERCPs were performed by a single experienced endoscopist (10

Strengths	Limitations
• Demographic characteristics, procedure time and indications for ERCP were similar across the treatment groups at baseline without a statistically significant difference. • The intervention and comparator were described well • Overall, the outcomes measures were valid and described clearly • The analysis was not based ITT population with no missing data. • The analysis of results used appropriate statistical methods, and actual probability values were reported for the findings. • Outcome data for the main findings were reported clearly, with estimates of random variability. • The authors declared no conflict of interest.	years' experience with ERCP) and an anesthesiologist. • Since the study was not powered for all outcomes, it is unknown if a larger sample size would produce different results. • It was unknown if the tool used to assess satisfaction with sedation was validated. • The study was conducted in a single center in Iran. Thus, the generalizability of the reported finding in the Canadian context is unknown
Goyal et al., 2016[2]	
• A partial-blind trial with the objective and hypothesis stated clearly. • Inclusion and exclusion criteria were stated, and calculations were performed beforehand to determine a sample size that ensured the study was adequately powered. for main outcome. • Demographic characteristics, procedure time and indications for ERCP appeared similar across the treatment groups at baseline. • The intervention and comparator were described well • Overall, the outcomes measures were valid and described clearly • The analysis of results used appropriate statistical methods, and actual probability values were reported for the findings. • Outcome data for the main findings were reported clearly, with estimates of random variability. • The authors declared no conflict of interest.	• The study was partially blinded with patients, researchers, nurses, and endoscopist blinded, but not the attending anesthesiologist. Therefore, a risk for bias existed due to potential for uneven approach to sedation rescue and other maneuvers. • It was unknown if the tool used to assess satisfaction with sedation was validated. • The analysis was not based on the ITT population since seven patients (three from the propofol–fentanyl and group and four from dexmedetomidine–ketamine) were excluded from the study because of missing data or procedure termination due to unrelated sedation reasons. It is unknow if that influence the findings • All the patients who participated in the study a BMI <30 kg/m^2. Thus, it is unknown is if the findings can be replicated in patients with a heavier build. • The study was conducted in a single center in India. Therefore, the generalizability of the reported finding in the Canadian context is unknown.
Zhang et al., 2016[5]	
• A double-blind trial with the objective and hypothesis stated clearly. • Inclusion and exclusion criteria were stated • The intervention and comparator were described well • Overall, the outcomes measures were valid and described clearly • The statistical analysis methods appeared appropriate and the results data were reported clearly, with estimates of random variability. • The authors declared no conflict of interest.	• Baseline demographic characteristics and procedure related parameter were reported without a p-value. Therefore, it was unclear whether they were statistically similar across the treatment groups. • Sample size calculations was not performed. Thus, it is unknown if a larger study population could produce different results. • According to the authors, the patients could be excluded from the final analysis if the endoscopist could not complete the procedure for any reason. However, there was no information about the number of patients screened or initially randomized. Thus, it was unclear if the analysis was based on the ITT population. • No information was provided about the missing data.

Strengths	Limitations
	• It was unknown if the tool used to assess satisfaction with sedation was validated. • Actual probability values were not reported for the findings. • The authors did not acknowledge limitations or consider any in the discussion and conclusions of their study. • The study was conducted in a single center in China. Therefore, the generalizability of the reported finding in the Canadian context is unknown.
Haytural et al., 2015[14]	
• A single-blind randomized controlled trial with the objective stated clearly. • Inclusion and exclusion criteria were stated, • Demographic characteristics, procedure time and indications for ERCP were similar across the treatment groups at baseline without a statistically significant difference. • The intervention and comparator were described well • Overall, the outcomes measures were valid and described clearly • The analysis of results used appropriate statistical methods, and actual probability values were reported for the findings. • Outcome data for the main findings were reported clearly, with estimates of random variability. • The authors declared no conflict of interest	• Although the gastroenterologist who performed the procedure and conducted outcome assessments was blinded to allocation of the sedative agents, it was not reported if other investigation staff and patients were also blinded. • Sample size calculations was not performed. Thus, it is unknown if a larger study population could produce different results. • The analysis was not based on ITT population. Two patients in propofol were excluded due to a drop in their oxygen saturation levels during the process. The impact of the missing data on the results was unknown. • Probability values were not uniformly reported, with p-values stated in general terms (i.e., $p > 0.05$ or $p< 0.05$) for some findings while others had actual p-values. • The authors did not acknowledge limitations or consider any in the discussion and conclusions of their study. • The study was conducted in a single center in Turkey. Therefore, the generalizability of the reported finding in the Canadian context is unknown.
Narayanan et al., 2015[15]	
• A single-blind trial using a block randomization design, • The objective of the study as well as the inclusion and exclusion criteria were stated clearly. • The demographic characteristics, procedure time, and indications for ERCP were similar for both the control and study groups, with no statistically significant differences. • The intervention and comparator were described well • Overall, the outcomes measures were valid and described clearly • The analysis of results used appropriate statistical methods, and actual probability values were reported for the findings. • Outcome data for the main findings were reported clearly, with estimates of random variability. • The authors declared no conflict of interest	• The study was partially blinded with patients, anesthetist blinded, but not the attending endoscopist. Therefore, a risk for bias existed due to potential for uneven approach to sedation rescue and other maneuvers. • Sample size calculations was not performed. Thus, it is unknown if a larger study population could produce different results. • The study included only low-risk patients with ASA PS I–III classification. Thus, the generalizability of the findings in the high-risk population that requires ERCP was unknown. • It was a pilot study and the doses of the sedative drugs had not been optimized for the ERCP procedure. • Patients' satisfaction was evaluated with unvalidated questionnaire.

Strengths	Limitations
Shin et al., 2015[6]	
• A registered randomized controlled trial with both participants and study team (except the anesthetist) blinded to the allocation. • The hypothesis of the study was clearly described along with inclusion and exclusion criteria of the study participants. • The primary and secondary endpoints of the study were valid and well defined. • Sample size calculation was done to ensure adequate power. • Characteristics of the study participants were reported. Potential confounders were compared between the two groups. Participants of both groups were recruited from same centers over the same period. • Interventions and comparator of the study were described in detail including doses, mode of administration and co-administered medications. • Outcome data for the main findings were reported and estimates of random variability was reported in the form of interquartile ranges. • Appropriate statistical tests were conducted to compare the groups, and actual probability values were reported for the findings. • The authors declared no conflict of interest	• The study was conducted in a single institution in China and enrolled only Asian patients. Thus, the generalizability of the findings in Canadian settings is unknown. • Analysis was not based on ITT population because 13 patients (seven in the conventional propofol-meperidine group and six in the propofol-fentanyl group) were dropped from analysis due to incomplete medical records or missing data at the time of analysis. The impact of the missing data on the reported data was unknown • The patients in the propofol-fentanyl group were significantly older than those of the conventional propofol-meperidine group (P = 0.025).
Song et al., 2015[16]	
• A randomized controlled trial with both participants and study team blinded to the allocation. • The hypothesis of the study was clearly described along with inclusion and exclusion criteria of the study participants. • The primary and secondary endpoints of the study were valid and well defined. • Sample size calculation was done to ensure adequate power. • Demographic characteristics and conditions of the study participants were similar across the two study groups. • Interventions and comparator of the study were described in detail including doses, mode of administration and co-administered medications. • Outcome data for the main findings were reported and estimates of random variability was reported in the form of interquartile ranges. • Appropriate statistical tests were conducted to compare the groups, and actual probability values were reported for the findings. • The authors declared no conflict of interest	• The study was conducted in a single institution and enrolled only Asian patients. Thus, the generalizability of the findings in Canadian settings is unknown. • Although survival was a stated outcome of interest of the study, survival analysis and results were not reported. Thus, the risk of selective reporting cannot be ruled out. • Patients with known severe respiratory disease (vital capacity and/or forced expiratory volume <50%) were excluded from this study.
Ebru and Resul, 2019[17]	

Strengths	Limitations
• Objective and hypothesis of study were stated • Inclusion and exclusion were provided. • The intervention and comparator were described clearly. • Outcomes of interest were stated clearly • Statistical tests appeared to be appropriate • The authors declared no conflict of interest and there was no external source of funding.	• Patients in the two treatment groups underwent the ERCP procedure in two different periods (midazolam-meperidine group in 2016 and propofol-ketamine group in 2018), which may be a reason for important differences that could affect outcomes. For example, the duration of the procedure differed between the treatment groups. Thus, it was unclear if changes healthcare delivery over the years could have influenced the reported results. • The inclusion criteria limited eligibility to participate in the study to patients who were at least 85 years old and with ASA III or IV. Thus, the generalizability in younger patients with lower risk (ASA I –II) was unknown. • There were inconsistencies between reported information in the text and some data in the provided tables (e.g., data in the tables did not reflect the similarities in some demographic characteristics and the duration of procedure as reported in the text). • A sample size was calculated was not performed and it was unclear if the study was adequately power for all outcomes • The authors did not report limitations or consider such in the discussion and conclusions of their study • The study was conducted in Turkey, therefore the generalizability of the findings in the Canadian context is unknown.

ASA PS = American Society of Anesthesiologists physical status; BMI = body mass index; ERCP = endoscopic retrograde cholangiopancreatography; IQR = interquartile range; ITT = intent-to-treat;

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Eberl et al., 2020[9]	
Total dose of propofol used • The median (IQR) total doses of propofol administered was statistically significantly lower in patients sedated with Propofol–Esketamine (PE) than those sedated with Propofol–Alfentanil (PA) (8.3 [6.2 to 10] versus 10.5 [7.9 to 12.5] mg/kg/hour; P<0.001). **Time to recovery** • There was no significant difference in the median (IQR) time to recovery between PE and the PA groups (69 [66 to 70.3] versus 69 minutes [63 to 72] minutes; P = 0.85). **Satisfaction score** • The median (IQR) patient satisfaction with the procedure was VAS 100 (80 to 100) for both groups (P = 0.812) • There was no significant difference between the PE and PA groups regarding whether the patient would recommend the sedation regimen (P=0.33). • The median (IQR) endoscopist satisfaction was 5 (4 to 5) in both groups (P=0.199). **Hypotension** • Hypotension occurred in 17 patients (21.5%) in the PA group versus 10 patients (12.0%) in the PE group. The difference of not statistically significant (P = 0.1). **Bradycardia** • Bradycardia was identified in two patients (2.5%) in the PA group versus three patients (3.6%) in the PE group. The difference of not statistically significant (P = 0.08). **Oxygen desaturation** • Desaturation was observed in eight patients (10.1%) in the PA versus 11 patients (13.3%) in the PE group. The difference of not statistically significant (P = 0.45).	• "Deep sedation with propofol TCI (Marsh model) and repeated bolus of low-dose esketamine significantly reduces total propofol requirement for ERCP in ASA PS I and II patients without effect on recovery time, endoscopists' and patients' satisfaction or cardiorespiratory adverse effects compared with a deep sedation regimen with propofol TCI (Marsh model) and repeated bolus alfentanil in the hands of well-trained sedation practitioners. P. 401"[9]
Sayed et al., 2019[10]	
Time to recovery • The mean (SD) time to recovery (i.e., to achieve BIS ≥ 90) was 6.25 (0.90) minutes in the propofol alone group versus 9.25 (2.17) minutes in the Propofol–Ketamine (PK) group. The difference was statistically significant (P = 0.00). **Pain during procedure** • The mean (SD) VAS pain score was 2.65 (1.23) in the propofol group versus 2.40 (1.22) in the PK group. The difference was not statistically significant (P = 0.123). **Satisfaction with sedation**	• "In conclusion, our study concluded that ketofol combination is equally effective for procedural sedation compared to propofol alone. CNS monitoring by BIS provided adequate depth of sedation which maintain hemodynamic stability, prevent respiratory depression or apnea, and prevent delayed recovery and challenges of sedation outside operating room in patients undergoing ERCP. There was clinical observed lag between subjective assessment of sedation (Ramsay sedation score) and objective assessment of sedation (BIS) with delay in BIS assessment in comparison with RSS for further studies on large number of population. The correlation

Main study findings	Authors' conclusion
• The overall patients' satisfaction with sedation was statistically significantly higher with propofol than PK (P =0.008). • 82.5% of patients in the propofol group rated satisfaction with sedation as perfect versus 52.5% in the PK group. • 17.5% of patients in the propofol group had good satisfaction versus 40% in the PK group. • 7.5% of patients in the PK group were moderately satisfied with sedation and no patient in the propofol gave a moderate score. • The difference in overall endoscopists' satisfaction with sedation with propofol or PK was not statistically significant (P = 0.239). • All the endoscopists (100%) had perfect satisfaction with sedation with propofol versus 92% with PK. 7.5% of endoscopist grated sedation with ketofol as good. **Hypotension** • Hypotension occurred in 2 patients (5%) in the propofol group versus no incident (0%) in the PK group. The difference of not statistically significant (P = 0.474). **Bradycardia** • Bradycardia was identified in 3 patients (7.5%) in the PK group versus no incident of bradycardia in the propofol group. The difference of not statistically significant (P = 0.239). **Oxygen desaturation** • Desaturation was observed in 2 patients (5%) in the propofol group versus 4 patients (10%) in the PK group. The difference of not statistically significant (P = 0.239). **Nausea and/or Vomiting** • Vomiting occurred in 3 patients (7.5%) in the PK group versus no incident (0%) in the propofol group. The difference of not statistically significant (P = 0.239). **Agitation** • Three patients (7.5%) in the PK group exhibited agitation versus no incident (0%) in the propofol group. The difference of not statistically significant (P = 0.239). **Hypersalivation** • Hypersalivation was observed in 2 patients (5%) in the propofol group versus 6 patients (10%) in the PK group. The difference of not statistically significant (P = 0.246).	between RSS and BIS with ketofol sedation need to be further studied." P. 7[10]
Lu et al., 2018[1]	
Depth of sedation by RSS • The RSS in the Dexmedetomidine–Remifentanil combination (DR) group was found to be higher than that in the Midazolam–Remifentanil combination (MR) group (P < 0.05).	• "In conclusion, DR provided high efficacy and a superior oxygenation profile during ERCP compared to a midazolam–remifentanil combination. Therefore, a dexmedetomidine substitute may be advantageous for oxygenation during sedation in therapeutic ERCP

Main study findings	Authors' conclusion
Additional drug uses • Overall, 6(5.6%) patients in the DR group received additional drugs during the procedure compared with 5 (5.8%) patients in the MR group. The difference between the two groups was statistically significant (P = 0.001). • The mean (SD) additional dosage of midazolam was statistically significantly higher in the MR group than the DR group (1.37 [0.3] mg versus 0.06 [.03] mg, respectively; P < 0.001) **Time to recovery** • The mean (SD) recovery times (i.e., to achieve SRS 6) were not statistically significantly different between the DR and MR groups (1.5 [3.6] minutes versus 0.9 [2.8] minutes, respectively; P = 0.247) **Pain during procedure** • Two patients (1.9%) in the DR group reported painful procedure compared with 6 (6.9%) in the MR group. The difference was statistically significant (P = 0.001). **Patients' and endoscopists' satisfaction** • Patients' satisfaction was significantly higher in the DR group than the MR group, with mean (SD) scores of 3.9 (0.3) versus 3.6 (0.7), P = 0.001. • Endoscopists' satisfaction scores were not statistically significantly different between the DR and MR groups, with a mean (SD) of 3.9 (0.4) in each group, (p = 0.403). **Mean arterial pressure** • The mean (SD) MAP values decreased from 104 (18) mmHg at baseline to 91 (10) mmHg at the end of the operation in the DR group compared with a decrease from 102 (16) mmHg to 99 (13) mmHg (baseline to end of procedure) for the MR group. The difference between the two groups was statistically significant (P = 0.001). **Heart rate** • At the end of the procedure, the mean (SD) heart rate values) in the DR group had decreased 84 (14) from a baseline value of 87 (19) bpm, whereas in the MR group there was an increase to 98 (14) from 83 (15) at baseline. The difference between the two groups was statistically significant (P = 0.008). **Respiratory rate** • The mean (SD) respiratory rate was 16 (1) both at baseline and the end of procedure in the DR group, whereas in the MR group there was an increase to 16 (1) at baseline to 17 (2) the end of the operation. The difference between the two groups was statistically significant (P = 0.001). **Oxygen desaturation** • Oxygen desaturation (SpO_2 < 90%) occurred 19 (22%) of patients in the MR group compared with none in the group. The difference was statistically significant (P = 0.001). Nausea and/or Vomiting	and may also be used as a valuable alternative to midazolam. P. 1639"[1]

Main study findings	Authors' conclusion
• Nausea and vomiting occurred in 7 (6.5%) of patients in the DR group compared with 2 (2.3%) of patients in the MR group. The difference was statistically significant (P = 0.001).	
Park et al., 2018[3]	
Respiratory event • Overall, respiratory events were identified in 10 patients (15.6%) in the etomidate group versus 16 patients (25.4%) in the propofol group. The difference was not statistically significant (P = 0.172). • The rate difference of -9.8% (1-sided 97.5% CI, -□ to 4.2%). Thus, etomidate was noninferior to propofol in terms of overall respiratory event because the upper bound of the 1-sided 97.5% CI lies below the noninferiority margin of 10%. • Significantly less patients in the etomidate group required airway intervention for adverse respiratory events than in the propofol group [(6 [9.4%] versus 14 [22.2%], respectively; P = 0.047) **Oxygen desaturation** • Oxygen desaturation was identified in 10 patients (15.6%) in the etomidate group versus 16 patients (25.4%) in the propofol group. The difference was not statistically significant (P = 0.172). **Time to Recovery** • The mean (SD) recovery times were not statistically significantly different between the etomidate and propofol groups (29 [10.3] minutes versus 31.8 [11.6] minutes, respectively; P = 0.176) **Satisfaction for sedation** • Most patients in both the etomidate and propofol groups were satisfied with the sedation during the procedure, with no statistically significant difference between the groups (93.8% vs. 96.8%, respectively; P = 1.000). • There was no statistically significant difference endoscopists' satisfaction rate with etomidate versus propofol (93.8% vs. 84.1%, respectively; P = 0.113). **Cardiovascular events** • The overall incidence of cardiovascular events was 43 (67.2%) in the etomidate group compared with 32 (50.8%) in the propofol group. The difference was not statistically significant (P = 0.060). • However, significantly more patients in the etomidate group had tachycardia compared to those in the propofol group (41 (64.1%) versus 22 (34.9%), respectively; P = 0.001) • A multivariable analysis for adverse events showed that etomidate had a higher overall risk of cardiovascular events compared with propofol (odds ratio for etomidate, 3.81; 95% CI, 1.68 to 9.08). • However, etomidate use was not an independent risk factor for overall adverse events that interfered with	• "Despite these limitations, our data provide a clearer understanding of a better sedative efficacy and safety of etomidate-based sedation for ERCP. Etomidate-based sedation was noninferior to propofol-based sedation in terms of the overall incidence of respiratory events during ERCP. Nurse-administered etomidate-based sedation may be an alternative option for ERCP in patients with ASA physical status I to II, especially in a clinical situation where an anesthesiologist is unavailable. P. 183"[3]

Main study findings	Authors' conclusion
the ERCP procedure (OR for etomidate, 0.52; 95% CI, 0.18 to 1.45). •	
Han et al., 2017[11]	
Time to recovery • The mean (SD) times to recovery after completion of the endoscopic procedures were 17.91 (6.29) minutes and 14.11 (4.46) minutes in the Propofol–Fentanyl (PF) and Midazolam–Fentanyl (MF) groups, respectively. The difference was statistically significant (P < 0.001). **Pain during procedure** • The mean (SD) pain scores 4.0 (1.0) in the MF 3.67 (0.81) versus in the propofol group. Five patients (10%) and six patients (12) in the MF and PF groups, respectively, experienced a sense of pain during the procedures. The differences were not statistically significant in either comparison (P ≥ 0.557). **Satisfaction with sedation** • There were no statistically significant differences in satisfaction with sedation between the MF and PF groups as rated by patients, and endoscopists. • The mean (SD) patient satisfaction score for sedation was 8.94 (1.51) in the MF group and 8.8 (2.10) in the PF group (P = 0.680). • The mean (SD) endoscopists' satisfaction score for sedation was 8.38 (1.53) in the MF group and 8.44 (1.31) in the PF group (P = 0.906). **Cardiopulmonary complications** • There were no statistically significant differences between the MF and PF groups in the overall cardiopulmonary AEs or individual AEs contributing to the overall. **Overall cardiovascular adverse events** • Overall cardiopulmonary AEs was identified in 12 patients (24%) in the MF group compared with 11 patients (22%) in the PF group. (P = 0.812). **Hypotension** • Systolic hypotension occurred in 2 patients (4%) in the MF group versus 3 patients (6%) patients in the propofol group (P = 0.648) **Bradycardia** • One patient in the PF group developed bradycardia versus no bradycardia in the MF group (P = 0.317). **Hypoxia** • Seven patients (14%) in the MF group had Hypoxia compared with in 8 patients (16%) in the PF group (P = 0.779).	• "Both midazolam and propofol, together with fentanyl-based endoscopic sedation, in patients over 80 years of age are safe and effective for therapeutic ERCP. Therapeutic outcomes and complications were also not different between the two compounds. In the usual practice of endoscopic sedation without anesthesiologists, propofol-based sedations were more effective than midazolam-based sedations without increasing complications. However, according to the age group, especially for those over 80 years of age, midazolam-based sedation has the same efficacy with a propofol-based sedation. Based on the availability of an antidote and the tendency for sedation safety, midazolam-based sedation may be preferred in patients over 80 years of age undergoing non-anesthesiologist-induced sedation. P. 375"[11]
Akhondzadeh et al., 2016[12]	
Effectiveness of sedation • The mean (SD) RSS, 90 seconds after the start the start of sedation, was not statistically significantly	• "A comparison between the two drugs combination shows that while both groups were similar in terms of the hemodynamic and sedation criteria, because of

Main study findings	Authors' conclusion
different between the PF and PK groups (4.42 [1.25] versus 4.51 [1.22]; P = 0.68]) • The mean (SD) total dose of propofol was not statistically different between the PF and PK groups (134.42 [63.66] versus 148.67 [71.24]; P = 0.36), which indicated that the patients in either group did not require significantly more sedation recue medication than the other group. **Hemodynamic indices** • There were no statistically significant differences between PF and PK treatment groups regarding systolic blood pressure, diastolic blood pressure, and heart rate during and after the procedure (P ≥0.25 in all comparisons). **Incidence of apnea** • Apnea occurred in 16 patients (32.7%) in the PK group and 31 patients (63%) in the PF group. The difference was statistically significant (P < 0.05).	the lower amount of pain and apnea in the PK group, the mentioned combination generally in the ERCP procedure is more efficient and more secure. In the end, the broader spectrum studies are recommended for investigating and comparing other medicinal combinations and their effects to perform more secure sedation. P. 148"[12]
Bahrami Gorji et al., 2016[13]	
Sedation quality • The mean (SD) RSS at 4 minutes was statistically significantly higher in the PK group than in the PF group (4.43 [0.57] versus 4.17 [0.45], respectively; P = 0.037). The score was also statistically significant at 15 minutes (P=0.035). • There difference in sedation scores between the treatment groups at other assessment points were not statistically significant time (P > 0.05). **Rescue dose of propofol** • There was no significant difference between the PK and the PF groups regarding the amount of propofol used as rescue. The mean (SD) doses were 41.00 (64.71) mg versus 30.95 (47.77) mg, respectively; P = 0.45). **Time to recovery** • There was no significant difference in the recovery time between the treatment groups. The mean (SD) time to Aldrete score 9 was 14.17 (4.56) minutes in the PK group versus 12.86 (3.34) minutes in the PF group (P = 0.164). **Satisfaction with sedation** • There was no significant difference between the PK and the PF groups regarding the patients' and endoscopists' satisfaction. • The mean (SD) patients' satisfaction score was 7.45 (2.79) in the PK group versus 7.46 (2.94) in the PF l group; P = 0.646). • The mean (SD) endoscopists' satisfaction score was 7.91 (1.24) in the PK group versus 7.93 (1.12) in the PF group; P = 0.317). **Hemodynamic indices** ▪ A plot of MAP against time showed that MAP at 8 minutes was statistically significantly higher in the PK	▪ "The sedative effects of propofol-fentanyl and propofol-ketamine were acceptable and equal. Pain after ERCP in the PF group was less than in the PK group. The frequency of apnea was higher in the PF group, but not significantly. Patient and endoscopist satisfaction and recovery time showed no differences between the two groups. Patients at risk of respiratory depression are recommended to receive a combination of propofol and ketamine. P. 6"[13]

Main study findings	Authors' conclusion
group than the PF group (P = 0.021). However, there was no significant difference in MAP between the treatment (P > 0.05). ▪ There was no statistically significant difference between the PK and the PF groups regarding respiratory rate, heart rate, and SPO_2 (P > 0.05 in all comparisons). **Mean arterial pressure** ▪ At 8 minutes, the PK group was significantly higher than in the PF group (P = 0.021), but at other times, there was no significant difference between the two groups (P > 0.05). **Heart rate** ▪ The mean heart rate in patients in the PK and PF groups showed no significant difference (P > 0.05). **Incidence of apnea** ▪ Apnea occurred in one patient (3.3%) in the PK group versus 7 patients (16.7%) in the PF group, including three who were intubated. The difference was not statistically significant (P = 0.128). **Nausea and/or vomiting** ▪ **O**ne patient **(3.3%)** in the PK group **versus 4** patients **(9.5%)** in the PF group had nausea and vomiting**. The difference was not** statistically significant (P = 0.257).	
Goyal et al., 2016[2]	
Time to recovery • The mean (SD) time to recovery was statistically significantly shorter in the PF group than the DK group (5 [5] minutes versus 10 [5] minutes, respectively; P < 0.001). **Endoscopist satisfaction** • Endoscopists rated the ERCP procedure as satisfactory score in 32 patients (76.2%) in the PF group versus 36 patients (87.8%) in the DK group. • Endoscopists graded the ERCP procedure as difficult in 10 patients (23.8%) in the PF group versus 5 patients (12.2%) in the DK group. • There were no impossible procedures in any of the treatment groups. **Hypotension** • The was no incident of hypotension among patients in DK group versus 8 patients (19%) in the PF group. The difference was statistically significant (95% CI 0.07 to 0.31; Fisher exact test). **Bradycardia** • The was no incident of bradycardia among patients in DK group versus 2 patients (4.7%) in the PF group. The difference was statistically significant (95% CI 0.0 to 0.31; Fisher exact test). **Oxygen desaturation** • The was no incident of desaturation among patients in DK group versus 18 patients (42.8%) in the PF group.	▪ "Overall, both drug combinations used in our study were effective for sedation for ERCP. The hemodynamic and respiratory profiles of the patients were better maintained with DK, but the recovery was faster with PF. P.932"[2]

Main study findings	Authors' conclusion
The difference was statistically significant (95% CI 0.28 to 0.58; Fisher test). **Respiratory depression** • The was no incident of respiratory depression among patients in DK group versus 5 patients (11.9%) in the PF group. The difference was statistically significant (95% CI 0.02 to 0.22; Fisher test). **Nausea and/or Vomiting** • Nausea was reported in 5 patients (11.9%) in the PF group versus 4 patients (9.7%) in the DK group • Vomiting occurred in 2 patients (4.7%) in the PF group versus 3 patients (7.3%) in the DK group	
Zhang et al., 2016[5]	
Pain during procedure • Five patients (15.2%) in the Midazolam-Meperidine (MM) conventional group reported pain during the procedure versus 3 patients (9.1%) in each of the remifentanil alone and Midazolam-Remifentanil (MR) groups. The difference was not statistically significant. **Endoscopists' and Patents' satisfaction** • The mean (SD) endoscopists' satisfaction score was 93.5 (5.8), 96.2 (4.7), and 94.9 (5.2) in the conventional, remifentanil alone, and MR groups respectively. The difference in the scores was statistically significant difference between the remifentanil alone and each of the conventional and MR groups (P< 0.05), but not between the conventional and RM groups. • The mean (SD) patients' satisfaction score was 98.4 (4.1), 98.9 (3.6), and 99.1 (3.7) in the conventional, remifentanil alone, and MR groups respectively. There were no statistically significant differences in patients' satisfaction between the treatment groups. **Hypotension** • Hypotension was identified in 2 patients (6.1%) of patients in the MM (conventional) group compared with none in the remifentanil alone group and 1 (3.0%) in the remifentanil-midazolam (RM) group **Bradycardia** • One patient (3.0%) in the RM group had bradycardia compared with no incident of bradycardia in either the conventional or remifentanil alone groups. **Respiratory depression** • Compared to the remifentanil alone group, the number of patients who experience respiratory depression was statistically significantly more in the conventional group (11 [33%] versus 3 [9.1%]; P< 0.05) and in the RM group (10 [20.3%] versus 3 [9.1%]; P< 0.05). **Apnea** • No patient in the remifentanil alone group experienced apnea compared with one patient (3.0%) and 4 patients (12.1%) in the conventional and RM groups, respective. Only the difference between the	▪ "In conclusion, conventional sedation, remifentanil infusion alone, and remifentanil/midazolam sedation can be used as a conscious sedation technique for ERCP, however, remifentanil infusion alone has a better recovery profile, physician satisfaction, and safety profile than remifentanil in combination with midazolam and conventional sedation techniques. ▪ That said, the type of anesthetic chosen should be individually tailored to the patient based upon medical history, physical exam, and assessment by qualified anesthetic personnel.

Main study findings	Authors' conclusion
remifentanil alone and the RM groups was statistically significant P< 0.05). **Nausea and/or Vomiting** • Nausea or vomiting occurred in 2 patients (6.1%) in the conventional group compared with 7 patients (21.2%) and 9 patients (27.3%) in the remifentanil alone and RM groups, respectively. Only the difference between the conventional and RM groups was statistically significant (P< 0.05).	
Haytural et al., 2015[14]	
Level of sedation • The differences in the quality of sedation between the propofol-fentanyl (PF) combination versus propofol–remifentanil (PR) combination versus propofol alone, as assessed by RSS, were not statistically significant either (P > 0.0033; Bonferroni corrections, where P < 0.0033 was the accepted statistically significant level) **Total dose of propofol** • The total dose of propofol administered was statistically significantly higher in the propofol alone group compared with either the PR group (375 versus 150 mg; P < 0.05) or the PF group (375 mg versus 245 mg; P < 0.001). • The total propofol doses administered was statistically significantly higher in the PF group than in the PR group (245 mg versus 150 mg; P < 0.05). **Gastroenterologist satisfaction** • The gastroenterologist rated satisfaction with the quality of surgery in 8 patients (27%) in the propofol alone l group as "Well" compared with 3 (10%) and 6 (20%) in the PR and PF groups, respectively. According to the authors, the difference was not statistically significant (p-value not reported). • The gastroenterologist (73.3%) rated satisfaction with the quality of surgery in 22 patients (73.3%) in the propofol alone group as "Very Well" compared with 27 (90%) and 24 (80%) in the PR and PF groups, respectively. According to the authors, the difference was not statistically significant (p-value not reported). **Hemodynamic stability** • There were no statistically significant differences between the groups regarding changes in systolic pressure, diastolic pressure, MAP, and saturation levels throughout the follow-up (P > 0.05).	• "In conclusion, while providing adequate sedation during ERCP, practitioners should avoid administering sedatives excessively and try to minimize the side effects associated with the administration of excessive sedatives. In line with the findings of our study, it can be said that administration of propofol in combination with an opioid rather than as a single agent to ERCP patients ensured effective and reliable sedation, reduced total dose of propofol, increased practitioner satisfaction, decreased the pain level, and ensured hemodynamic stabilization. We consider remifentanil as the most appropriate opioid agent because it reduces the pain level and the amount of propofol to be administered to the greatest extent and is not different from other agents in terms of side effects. P. 5"[14]
Narayanan et al., 2015[15]	
Time to normal activity • The median (IQR) time it took for patients to resume normal activity was 19.5 (5, 26) hours in the Midazolam–Pethidine (MPt) conventional group versus 20 (4, 27) hours within the Midazolam–Ketamine (MK) group **Satisfaction with sedation**	▪ "In this pilot study in an average patient population, none of whom were particularly compromised or at risk, it was not possible to demonstrate an advantage for ketamine-based sedation in terms of respiratory or circulatory function. But sedation during endoscopy with ketamine and midazolam was as acceptable to patients as conventional sedation and was not

Main study findings	Authors' conclusion
▪ On a 0 to 4 satisfaction scale (0 = very dissatisfied, 4 = very satisfied), the median (IQR) patients' satisfaction with sedation score was 3.5 (1, 4) with MPt and 4 (2, 4) in the MK group. The difference was not statistically significant (P = 0.88) **Pain experienced during procedure** • On a 0 to 4 pain scale (0 = none, 4 = very severe), the median (IQR) pain score during the ERCP procedure was 0 (0, 2) with MPt and 1 (0, 3) in the MK group. The difference was not statistically significant (P = 0.82) **Nausea and/or Vomiting** • Two patients (11%) in the MPt experienced nausea versus 3 patients (16%) in the MK group • Vomiting occurred in 2 patients (11%) in each of the of the treatment groups	associated with emergence reactions or clinically significant cardiovascular effects. Equivalent sedation for endoscopy was achieved using similar amounts of midazolam, but in conjunction with a drug which might be expected to preserve blood pressure and respiratory drive, and maintain airway reflexes, when compared to the opioids conventionally used. Larger studies would be needed before considering ketamine for general use, but it does show potential as an agent for sedation during endoscopy. P. 1302"[15]
Shin et al., 2015[6]	
Time to recovery • The median (IQR) time to full recovery (i.e., MAS = 10) in the conventional Propofol–Meperidine (PM) group and the Propofol–Fentanyl (PF) group were not statistically significantly different (13 [5, 20] versus 12 [5, 19] minutes, respectively; P = 0.662] **Satisfaction scores** ▪ The median (IQR) endoscopists' satisfaction score was the same (90 [80, 100]) for both the PM and PF groups (P = 0.868). ▪ The median (IQR patients' satisfaction scores were also not different between the conventional PM and PF groups (90 [90, 100] versus (90 [80, 100]), respectively; P = 0.890) **Hypotension** • The number of patients that presented with significant hypotension in the conventional PM group versus the PF group was not different between the two groups. (9 [9.0%] versus 11 [10.8%], respectively; P = 0.671). **Bradycardia** • The number of patients had bradycardia in the conventional PM group was not statistically significantly different from that in the PF group (4 [4.0%] versus 3 [2.9%], respectively; P = 0.681). **Oxygen desaturation** • Two patients (2.0%) in the conventional PM group and 3 patients (2.9%) in the PF group experienced desaturation (P = 0.287).	▪ "In conclusion, combining repeated doses of fentanyl for adequate pain control with continuous propofol infusion does not seem to prolong recovery times compared to a single dose of meperidine followed by continuous propofol infusion. The resulting decrease in overall propofol dose may have more significance in patients with poor general conditions which are not uncommon with ERCP. Considering the pharmacologic characteristics of the two opioids and the trend of higher satisfaction levels of the endoscopists and patients, combination sedation using repeated administrations of fentanyl with propofol infusion may be a safer and more effective sedation method compared to conventional BPS with meperidine during ERCP. P. 9"[16]
Song et al., 2015[16]	
Time to recovery • The mean (SD) time to full recovery (i.e., MAS = 10) in the etomidate group and the propofol group were not statistically significantly different (14.5 [9.3] minutes versus 15.2 [6.1] minutes, respectively; P = 0.702]	▪ "In conclusion, our study demonstrated that etomidate anesthesia during ERCP caused more stable haemodynamic responses compared with propofol. Etomidate is an alternative to propofol during ERCP. P. 564"[16]

Main study findings	Authors' conclusion
Satisfaction scores ▪ The mean (SD) gastroenterologists' satisfaction score was the same (3.8 [0.4]) for both the etomidate and propofol groups (P = 1.000). ▪ The median (IQR patients' satisfaction scores were also not different between the etomidate and propofol groups (3.8 [0.4] versus (3.8 [0.3]), respectively; P = 0.419). **Change in MAP and heart rate from baseline** • The mean (SD) percent change from baseline MAP was -8.4 (7.8) and -14.4 (9.4) in the etomidate group and the propofol group, respectively. The difference was statistically significant (P = 0.002). ▪ The mean (SD) percent change from baseline heart rate was 1.8 (16.6) and 2.4 (16.3) in the etomidate group and the propofol group, respectively. The difference was not statistically significant (P = 0.874). **Hypotension** • The number of patients that had significant hypotension was the same (1 [2.5%]) in both the etomidate and the propofol groups (P = 1.000). **Bradycardia** • There was no incidence of bradycardia in either of the treatment groups. **Oxygen desaturation** • There was no incidence of oxygen desaturation in either of the treatment groups. **Apnea** • There was no incidence of apnea in either of the treatment groups. **Nausea and/or Vomiting** • Nausea and vomiting occurred in one patient (1.2%) in each of the two treatment groups (P = 1.000) • There were no statistically significant differences in pain scores between the two groups at the 12-, 18-, or 24-hour assessment points.	
Ebru and Resul, 2019[17]	
Time to achieve targeted sedation • The mean (SD) time to achieve RSS scores ≥ 4 was statistically significantly longer in the Midazolam–Meperidine (MM) conventional group than the Propofol–Ketamine (PK) group (5.41 [0.49] minutes versus 3.21 [0.41] minutes, respectively; P < 0.001) **Amount of rescue medication** • The mean (SD) dose of propofol used as recue sedation medication was statistically significantly higher in the MM group than the PK group (12.15 [0.56] mg versus 10.32 [0.62] mg, respectively; P < 0.001) **Time to recovery** • The mean (SD) time to recovery (i.e., to achieve MAS ≥9) was statistically significantly higher in the MM	▪ "Ketofol is more effective and safer than the combination of midazolam and meperidine in order to achieve adequate sedation in ERCP patients in a shorter period of time with lower doses. Ketofol provides better hemodynamic stability and results in lower rates of nausea/vomiting and respiratory complications than does midazolam-meperidine. We believe that ketofol is a better choice than the combination of midazolam and meperidine for patients who need a shorter period of induction at the onset of sedation. Ketofol is a safe alternative to conventional sedation regimens during ERCP for oldest old patients. P. 762"[17]

Main study findings	Authors' conclusion
group than the PK group (11.11 [0.31] minutes versus 10.93 [0.25] mg, respectively; P < 0.001) **Bradycardia** • The number of patients in whom bradycardia was identified during the procedure was statistically significantly more in the MM group than the PK group (17 [22.7%] versus 2 [2.7%], respectively; P < 0.05**)** **Hypotension** • There was no statistically significant difference between the MM and PK groups in the number of patients who had hypotension during the procedure (3 [4.0%] versus 1 [1.3%] respectively; P = 0.300) **Oxygen desaturation (SpO2 < 90 mmHg),** • There was no statistically significant difference between the MM and PK groups in the number of patients in whom oxygen desaturation occurred during the procedure (13 [17.3%] versus 9 [12.0%] respectively; P = 0.356) **Apnea** • The number of patients who had apnea during the procedure was statistically significantly more in the MM group than the PK group (22 [29.3%] versus 3 [4.0%], respectively; P < 0.05)	

AE = adverse event; ASA PS = American Anesthesiology Association Physical Status; BIS = Bi-Spectral index; BPS = balanced propofol sedation; CI = confidence interval; CNS = central nervous system; DR = dexmedetomidine-remifentanil combination; ERCP = endoscopic retrograde cholangiopancreatography; PF= propofol-fentanyl combination; IQR = interquartile range; Ketofol = ketamine-propofol combination; MAP = mean arterial pressure; MR = midazolam-remifentanil combination; OR = odds ratio; PK = propofol-ketamine combination; RSS = Ramsey Sedation Score; SD = standard deviation; SPO_2 = oxygen saturation; TCI = target control infusion; VAS = visual analogue scale.