

Up-to-date literature review and issues of sedation during digestive endoscopy

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Abstract

Sedation is common during digestive endoscopy to provide comfort and pain relief for patients. However, the use of sedation in endoscopy also poses potential risks, and recent issues have been raised regarding its safety and administration. This literature review paper will discuss the most recent developments in the field of sedation in digestive endoscopy, including the adverse events that might be associated with sedation and how to manage it, the legal issues associated with administration, the impact of COVID-19 on sedation practices, and sedation in special situations. It will also touch upon the current guidelines and recommendations for sedation, including the importance of patient selection and monitoring and the need for training and certification for endoscopists administering sedation. The review will also analyse studies evaluating the safety and efficacy of various sedation techniques, including propofol, midazolam, and others. It will examine the benefits and drawbacks of these agents.

Key words: gastrointestinal, sedation, anaesthesia, propofol, COVID-19, legal, complications, adverse events, midazolam.

Introduction

Digestive endoscopy is a medical procedure used to diagnose and treat various conditions of the digestive tract. It involves the insertion of a thin, flexible tube with a light and camera at its tip into the digestive tract. This allows the doctor to view the inside of the digestive tract and take biopsies if needed. The most common type of digestive endoscopy is an upper endoscopy, which is used to examine the oesophagus, stomach, and duodenum. Other endoscopies include colonoscopies, sigmoidoscopies, and endoscopic retrograde cholangiopancreatography (ERCP). These procedures diagnose and treat conditions such as ulcers, polyps, tumours, and bleeding in the gastrointestinal tract [1].

Sometimes, sedation may be necessary for a patient undergoing a digestive endoscopy. Sedation can help reduce anxiety and discomfort during the procedure. The type of sedation used depends on the patient's age, medical history, and other factors [2, 3]. Many sedatives were validated and reported for digestive endoscopy, including midazolam, propofol, fentanyl, meperidine, and others (Table I). The doctor will discuss with the patient which type of sedative is best for them before administering it. In general, digestive endoscopy is considered safe when performed by experienced personnel using appropriate sedation techniques [4, 5]. However, there are many issues with sedatives for digestive endoscopic procedures, such as adverse events, sedation considerations for different populations, and legal

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Table 1. Characteristics of currently reported drugs for sedation in digestive endoscopic procedures

Drug	Advantages and uses	Disadvantages and limitations	Mechanism of action	Metabolism	Status of use in endoscopy	Standard dosing*
Oliceridine	Rapid onset and short duration of action; minimal respiratory depression; low risk of hypotension; minimal cardiovascular effects; no need for premedication; no need for a reversal agent	Limited clinical experience; potential for abuse and misuse	Activation of mu-opioid receptors in the brain and spinal cord, resulting in analgesia and sedation	Metabolized by the liver via CYP3A4 enzymes	Approved by the FDA for use in endoscopy	0.35 mg IV over 15 s, with a maximum dose of 1.05 mg/h
Fentanyl	Rapid onset and short duration of action; minimal respiratory depression; low risk of hypotension; minimal cardiovascular effects; no need for premedication; no need for a reversal agent	Potential for abuse and misuse due to its high potency; can cause respiratory depression if not monitored closely	Activation of mu-opioid receptors in the brain and spinal cord, resulting in analgesia and sedation	Metabolized by the liver via CYP3A4 enzymes	Approved by the FDA for use in endoscopy	0.5–2 µg/kg IV over 15 s, with a maximum dose of 12 mcg/kg/h
Diphenhydramine	Rapid onset and short duration of action; minimal respiratory depression; low risk of hypotension; minimal cardiovascular effects; no need for premedication or reversal agent	Can cause drowsiness, confusion, dry mouth, blurred vision, constipation, urinary retention, tachycardia, or arrhythmia if not monitored closely or taken at high doses	Blocks histamine receptors in the brain to produce sedative effects without causing significant respiratory depression or hypotension	Metabolized by the liver via CYP3A4 enzymes	Approved by the FDA for use in endoscopy as an adjunct to other drugs, such as fentanyl or midazolam, to reduce anxiety and agitation during procedures that require conscious sedation or general anaesthesia	25–50 mg IV over 5 min with a maximum dose of 100 mg/h depending on patient size and condition
Etomidate	Rapid onset and short duration of action; minimal respiratory depression; low risk of hypotension; minimal cardiovascular effects; no need for premedication; no need for a reversal agent	Can cause pain on injection, myoclonic movements, nausea, vomiting, bradycardia, hypertension, adrenal suppression, seizures, delirium	Inhibits GABA receptor activity resulting in sedation without causing significant respiratory depression or hypotension	Metabolized by the liver via CYP3A4 enzymes	Approved by the FDA for use in endoscopy as an adjunct to other drugs, such as fentanyl or midazolam, to reduce anxiety and agitation during procedures that require conscious sedation or general anaesthesia	0.3–0.6 mg/kg IV over 30 s with a maximum dose of 2 mg/kg/h, depending on patient size and condition

Table 1. Cont.

Drug	Advantages and uses	Disadvantages and limitations	Mechanism of action	Metabolism	Status of use in endoscopy	Standard dosing*
Local anaesthetics (e.g. Lidocaine)	Rapid onset and short duration of action; minimal respiratory depression; minimal cardiovascular effects; low incidence of nausea and vomiting; no active metabolites; can be used as an adjunct to other sedatives or analgesics for pain control during endoscopy procedures	Potential for allergic reactions or toxicity if administered incorrectly or at too high a dose; potential for local tissue damage if administered incorrectly or at too high a dose	Blocks nerve conduction by binding to sodium channels on nerve cells, resulting in local anaesthesia and analgesia without systemic effects when administered topically or locally into tissues near nerves (e.g. epidural)	Metabolized by the liver and excreted in the urine as inactive metabolites (metabolites may accumulate with repeated dosing)	Commonly used as an adjunct to other drugs during endoscopic procedures requiring pain control (e.g. ERCP)	1–3 mg/kg IV bolus followed by 0–1 mg/kg/h IV infusion (depending on procedure)
Ketamine	Rapid onset and short duration of action; minimal respiratory depression; minimal cardiovascular effects; low incidence of nausea and vomiting; no active metabolites	Potential for emergence reactions, including hallucinations, confusion, agitation, and delirium; potential for increased intraocular pressure leading to glaucoma or optic nerve damage	NMDA receptor antagonist that binds to receptors in the brain, resulting in sedation and analgesia	Metabolized by the liver and excreted in the urine	Commonly used for endoscopic sedation	0.5–1 mg/kg IV bolus followed by 0.25–0.5 mg/kg/h IV infusion or 2–4 mg/kg IM injection (depending on the procedure)
Dexmedetomidine	Rapid onset and short duration of action; minimal respiratory depression; minimal cardiovascular effects; low incidence of nausea and vomiting; no active metabolites; can be used as an adjunct to other sedatives or analgesics	High cost; potential for bradycardia and hypotension; potential for rebound hypertension after discontinuation	α_2 agonist that binds to receptors in the brain, resulting in sedation and anxiolysis	Metabolized by the liver and excreted in the urine	Commonly used for endoscopic sedation	0.2–0.7 μ g/kg/h IV infusion

Table I. Cont.

Drug	Advantages and uses	Disadvantages and limitations	Mechanism of action	Metabolism	Status of use in endoscopy	Standard dosing*
Remifentanyl	Fast onset and offset of action, predictable pharmacokinetics, flexible dosing, rapid titration, and minimal residual sedation	Respiratory depression, hypotension, and pruritus are potential adverse effects, as well as dependence, withdrawal, and tolerance	Remifentanyl is a mu-opioid receptor agonist which acts by modulating pain transmission and producing sedation	Rapid metabolic clearance by non-specific blood and tissue esterases, leading to a short elimination half-life	Commonly used for sedation in endoscopic procedures	Doses are titrated to effect, usually starting at 0.05–0.1 µg/kg/min and adjusted as needed to maintain the desired level of sedation
Midazolam	Rapid onset and short duration of action; minimal respiratory depression; low cost; good patient acceptance	Respiratory depression; prolonged recovery time; risk of oversedation	GABA agonist, binds to benzodiazepine receptors in the CNS, resulting in sedation and anxiolysis	Hepatic metabolism via the CYP3A4 enzyme system	Commonly used for moderate sedation in endoscopy	0.02–0.04 mg/kg IV over 2–3 min, with additional doses as needed up to 0.1 mg/kg
Propofol	Rapid onset and short duration of action; minimal respiratory depression; good patient acceptance	Risk of oversedation; prolonged recovery time; high cost	GABA agonist, binds to benzodiazepine receptors in the CNS, resulting in sedation and anxiolysis	Hepatic metabolism via the CYP3A4 enzyme system	Commonly used for deep sedation in endoscopy	1–2 mg/kg IV over 2–3 min, with additional doses as needed up to 4 mg/kg
Remimazolam	Rapid onset and offset of action, predictable pharmacokinetics, minimal residual sedation, and no active metabolites	Respiratory depression, hypotension, and pruritus are potential adverse effects, as well as dependence, withdrawal, and tolerance	Remimazolam is a short-acting benzodiazepine that acts by enhancing the inhibitory neurotransmitter GABA	Rapidly metabolized by esterases in the blood and tissues	Increasing use for sedation in endoscopic procedures	Doses are titrated to effect, usually starting at 0.25–0.5 mg, and adjusted as needed to maintain the desired level of sedation
Meperidine	Analgesic effect, rapid onset and offset of action, and low cost	Potential for adverse effects such as nausea, vomiting, confusion, hallucinations, and respiratory depression, as well as dependence, withdrawal, and tolerance	Meperidine is a synthetic opioid analgesic that acts by binding to mu, kappa, and delta opioid receptors in the central nervous system	Metabolized by the liver and excreted in the urine	Limited use in endoscopy due to its adverse effects and potential for toxicity	Usually administered intravenously at a dose of 50–100 mg

*Doses might be remarkably variable and should be decided according to endoscopists and/or anaesthesiologists based on their assessment of each case.

issues. Such issues might impact the validity and utility of these modalities, and they are continuously updated.

Aim

We aimed to conduct an up-to-date comprehensive literature review to discuss sedation for digestive endoscopy and related issues. We will discuss the impact of COVID-19 on sedation practices and how relevant issues can be solved to enhance this practice. Moreover, we will shed more light on sedation practices in special situations, the safety of the different sedatives, and the legal and economic issues reported in the literature during sedation for digestive endoscopic procedures.

Material and methods

This study is a literature review aiming to provide an insight about the recent updates in sedation for digestive endoscopy and to discuss the related issues. We aimed to include all studies discussing the following points: 1) the impact of COVID-19 on sedation during digestive endoscopy; 2) safety and adverse events of sedation; 3) sedation in special situations (e.g. during pregnancy and lactation, for children, the obese, the elderly, patients with coeliac disease, and those undergoing advanced procedures); 4) costs and economic issues of sedation; and 5) legal issues associated with sedation. We conducted a comprehensive search strategy of different databases, including PubMed, Embase, and Web of Science, to retrieve all relevant articles discussing the current issues and the used relevant keywords. No restrictions were made to the search strategy regarding publication data, country, language, or type. However, we mainly aimed to discuss more updated articles and guidelines. We also included review articles to compare their findings because they usually present comprehensive findings.

Impact of COVID-19

There has been growing evidence that the impact of COVID-19 on sedation practices has resulted in both positive and negative effects on patient outcomes [6, 7]. On one hand, the reduction in the use of deep sedation has been shown to decrease the risk of adverse events such as respiratory depression and aspiration and reduce the need for intensive care unit admissions [8, 9]. In addition, the shift to-

wards conscious sedation has been associated with improved patient satisfaction [8, 10, 11]. While conscious sedation may be a safer option in the context of the pandemic, it is crucial to recognize that this approach may not be appropriate or feasible for all patients, particularly those with significant anxiety or pain. To optimize sedation practices in the context of COVID-19, it is essential for endoscopists to carefully consider each patient's specific needs and risks and the characteristics of the endoscopic procedure. This may include using alternative sedation methods, such as midazolam, or developing new technologies or techniques to improve patient safety and comfort. Additionally, endoscopists should continue adhering to guidelines and recommendations for sedation administration, including patient monitoring and personal protective equipment. Overall, the impact of COVID-19 on sedation practices in digestive endoscopy underscores the importance of evidence-based decision-making and the need for continued research and innovation in this field [7, 12].

While some endoscopists view the changes in sedation practices due to COVID-19 as a necessary step towards improving patient safety, others have expressed concerns about the impact of these changes on patient outcomes and the quality of endoscopic procedures. Some endoscopists argue that the reduction of the use of deep sedation has resulted in increased patient discomfort and anxiety, longer procedure times, and a reduction in endoscopist experience and skill [7]. Additionally, some endoscopists have raised concerns about the impact of the COVID-19 pandemic on patient access to endoscopic procedures, particularly for those with significant medical conditions that require sedation. The reduction in the number of endoscopy procedures performed due to the pandemic has led to a backlog of patients waiting for care, which may result in delays in diagnosis and treatment for some individuals [7]. Finally, some endoscopists have expressed concerns about the impact of the COVID-19 pandemic on the financial stability of endoscopy practices, because the shift towards conscious sedation and the reduction in the number of procedures performed has resulted in decreased revenue for many practices [7].

In conclusion, the impact of COVID-19 on sedation practices in digestive endoscopy has been a topic of debate among endoscopists, with some viewing the changes as necessary for patient safety and others expressing concerns about the impact on

patient outcomes and endoscopy practices. Further research and collaboration among endoscopists and healthcare providers are needed to determine the most effective approaches for managing sedation in the context of the pandemic.

Safety and adverse events

The safety of sedation in digestive situations is generally considered good, but it is important to be aware of the potential complications and take steps

Table II. Different methods of sedation that can be used for digestive endoscopic procedures

Variables	Conscious sedation	Moderate sedation	Deep sedation	General anaesthesia
Advantages	Minimal risk of respiratory depression and other adverse events; patient remains awake and able to communicate; no need for intubation and extensive monitoring; quick recovery	Reduced level of consciousness and pain sensitivity; quick recovery	Complete loss of consciousness and pain sensitivity; quicker procedure time; no need for extensive monitoring	Complete loss of consciousness and pain sensitivity; rapid onset of effect; shorter recovery time compared to deep anaesthesia
Disadvantages	May cause discomfort and anxiety; requires experienced and trained personnel	Risk of adverse events increases with deeper levels of sedation; requires experienced and trained personnel	Requires more skill and experience from the endoscopist; longer recovery time; increased risk of complications due to deeper sedation	Requires more skill and experience from the endoscopist; increased risk of complications due to deeper sedation; longer recovery time compared to conscious sedation
Drugs used	Midazolam, Propofol, Fentanyl, Alfentanil, Remifentanil, Dexmedetomidine	Benzodiazepines (e.g., midazolam, lorazepam), opioids (e.g., fentanyl, morphine), and propofol	Midazolam, Propofol, Fentanyl, Alfentanil, Remifentanil, Dexmedetomidine	Propofol and other anaesthetic agents, such as etomidate and ketamine, are commonly used in combination with opioids and benzodiazepines for GA in endoscopy procedures
Complications	Hypoxia, hypotension, bradycardia, nausea/vomiting	Respiratory depression, hypotension, and bradycardia. Other rare but serious complications include aspiration, airway obstruction, and cardiac arrest	Hypoxia, hypotension, bradycardia, nausea/vomiting	Hypoxia, hypotension, bradycardia, nausea/vomiting
Satisfaction	High	High	High	High
Costs	Low	The cost of moderate sedation varies depending on the type of drug used and the length of the procedure. Generally, it is more expensive than minimal sedation but less expensive than deep sedation or general anaesthesia	Moderate	Higher cost than conscious and deep sedation due to additional equipment and personnel required for GA administration and monitoring of vital signs during the procedure
Intubation	No need	No needed	May be needed	Often needed
Patient responds	to verbal stimulation (normal)	To verbal or tactile stimulation (purposeful)	To repeated or painful stimuli (purposeful)	No response
Impact on cardiovascular	No impact	Minimal	Minimal	High risk of impaired functions

to minimize them. It should be noted that the risk of complications is highly variable based on the type of sedation (Table II). Overall, digestive endoscopy can be associated with complications in 0.02% to 0.54% of the cases, with an estimated mortality rate of 0.27%. Among these complications, it has been estimated that sedation-related cardiopulmonary complications occur in 0.0014% of these cases. An increased risk of developing these complications is observed among patients with comorbidities, and the incidence does not usually differ between non-anaesthetist and anaesthetist clinicians. Various complications have been reported, mainly bronchopulmonary aspiration, vasovagal events, arrhythmia, hypotension, and hypoxaemia [13–16].

Among the different complications, estimates indicate that cardiopulmonary complications are the most serious and common. For instance, a US nationwide investigation of 300,000 procedures showed that cardiopulmonary complications occurred in 0.9% of the cases [17]. Hypotension is another adverse event that might develop with sedation during digestive endoscopic procedures. The event does not usually have relevant clinical implications. It usually develops secondarily to propofol administration and combined administration of painkillers with sedatives [18]. Intravenous fluid and electrolyte infusion can adequately manage these events. Another study by Ljubicić *et al.* [19] also showed that 11.8% and 5.5% of their population sedated by propofol had a temporarily decreased heart rate of < 50 beats/minute and reduced O₂ saturation of < 85%, respectively. Arrhythmia is another cardiac complication that might develop in 4% to 72% of cases. Different clinically related arrhythmias, such as ectopic rhythms, bradycardia, extrasystoles, and sinus tachycardia, might develop, and sinus tachycardia is usually the commonest. Different risk factors were reported, including anxiety, endoscopy type, comorbidities like cardiac diseases, and the patient's age. In 4–42% of cases, electrocardiogram changes, mainly ST segment alterations, can be observed [5]. It has been shown that such alterations are not related to ischaemia and do not change following oxygen administration. Finally, atropine should be administered in cases of bradycardia.

Another common complication is hypoxaemia or oxygen desaturation, usually recorded when oxygen saturation (satO₂) is less than 90%. The estimated incidence is highly variable between 4% and 50%.

Hypoxaemia may be the most common event due to cases underestimation. Oral endoscopy significantly increases the risk of hypoxaemia due to potential laryngospasm, compressed airways, and the need for a deeper level of sedation. The risk of respiratory depression might also increase with the combined administration of opiates and benzodiazepines [20–23]. A previous study showed that the incidence of desaturation was < 10% during endoscopy-related propofol sedation with monitoring and oxygenation [24]. Moreover, there was a marginal need for endotracheal intubation. Evidence from various guidelines of different national scientific societies shows that oxygen supplementation is recommended during endoscopic procedures. However, oxygen administration might lead to increased hypercapnia and delayed apnoea recognition. Accordingly, using capnography and a pulse oximeter are recommended for adequate monitoring [16, 17].

The first step in managing desaturation is discontinuing the sedative agent, and oxygen flow should be increased to stimulate the patient. Moreover, secretion aspiration, securing the airway by jaw thrust, and using a Guedel tube might be necessary in certain situations. Antidotes like naloxone and flumazenil might be required in cases of desaturation induced by opiates and benzodiazepines administration [5]. Ventilation and oxygen masks might also be required in persistent and severe desaturation cases. However, only around 0.1% of cases with desaturation require ventilation. In cases when these measures fail, other respiratory resuscitation approaches, like orotracheal intubation and laryngeal masks, should be initiated [25–29]. Aspiration might also develop in 0.1% of cases following sedation. Patients with associated gastric retention and upper gastrointestinal tract bleeding are more liable to developing bronchopulmonary aspiration. Accordingly, orotracheal intubation should be performed amid endoscopy [27–29]. Propofol contamination and multidose containers might also lead to a potentially severe complication, i.e. the transmission of viral, bacterial, and fungal infections. Phlebitis might also be observed at a lower frequency. However, the risk increases when intravenous administration is done through small-calibre veins. Venous wall pain and swelling might develop following the administration of some propofol preparations, and lidocaine can effectively intervene against it [16, 23, 25, 27, 28].

Various risk factors have been reported to predispose to the development of cardiopulmonary complications. Some of these factors are patient-related and include old age (> 70 years old), decreased O₂ saturation (< 95%), ASA III and IV, hospitalization, associated lung diseases, and having a history of arrhythmia and ischaemic heart diseases [17, 20, 30–32]. Other factors are procedure related and are usually associated with oral endoscopy, emergency procedures, the status of O₂ administration, and drug dosage [33–36]. Therefore, relevant national guidelines from different societies recommend looking for these factors before sedation, to reduce the risk of complications and enhance management practices [5, 25].

It should be noted that the impact of procedure-related factors on developing complications is controversial. A previous investigation showed that the complication rate did not significantly differ between cirrhotic patients sedated with propofol with fentanyl or midazolam with fentanyl for upper gastrointestinal endoscopy (14% vs. 7.3%, respectively) [21, 37]. The rate of complications in another study did not differ between moderate sedation via meperidine/midazolam and deep sedation via propofol (1% vs. 0.6%, respectively). On the other hand, Amornyotin *et al.* [38] indicated that the complication rate was significantly higher with undiluted versus diluted propofol used for ERCP (42.9% vs. 18.2%, respectively).

Sedation in special situations

Special attention is required in various situations before sedation in relation to the endoscopic procedure. Consideration of the efficacy and safety of sedatives is essential in these events.

Pregnancy and lactation

Endoscopists should be aware of the potential risks and adverse events that might affect materno-foetal outcomes. Therefore, pregnant women should be monitored and evaluated before the procedure by intermittent blood pressure evaluation, pulse oximetry, and electrocardiography. Currently, there is no evidence of premature labour following sedation. However, the risk of foetal hypoxia secondary to sedation should also be considered [39]. Another important risk originates from maternal exposure to radiation during ERCP procedures. Therefore, avoid-

ing sedation for endoscopic procedures or dose reduction should be attempted. It has previously been reported that using midazolam might be the safest option for pregnancy [39–48].

Overall, ERCP in pregnancy is rarely done. However, it can be performed in dilated bile ducts, abnormal liver function tests, and recurrent biliary colic. Moreover, a previous study demonstrated that ERCP could be effectively and safely conducted during pregnancy [49, 50]. The risk of sedation over the foetus and the mother is uneventful and unpredictable. However, estimates show that post-ERCP pancreatitis is more common among pregnant women than in the general population [51, 52]. This was indicated even with cases requiring biliary stent placement. Finally, relevant data suggest the efficacy and safety of midazolam sedation for upper gastrointestinal endoscopy and flexible sigmoidoscopy [53–55], and some authors even stated that it the preferred choice for pregnant women [4]. However, these should be limited to cases with strong indications. Although colonoscopy is safe, data suggest that it should be conducted within the second trimester only with a strong indication [49, 53, 56–59].

Lactating women respond to sedation similarly to adults [42]. Studies indicate that various sedatives can be safely administered during lactation with minimal or no risk over infants. However, some recommendations should be considered [60, 61]. For instance, fentanyl should be preferred over meperidine because of its low concentration in breast milk [62–64]. On the other hand, meperidine usually concentrates in milk leading to infantile adverse events, such as interference with feeding and decreased infant alertness [60, 65, 66]. Propofol is concentrated in 0.015% of plasma levels in breast milk. Moreover, Breastfeeding should also be done at least 4 h after the administration of midazolam [64].

Children

Digestive endoscopy is a commonly performed procedure in paediatric patients, and sedation is often used to facilitate the procedure and reduce patient discomfort. Sedation can be administered in various forms, including oral, inhalational, and intravenous routes. According to current evidence, oral midazolam is a safe and effective option for sedation during paediatric gastrointestinal endoscopy [67–70]. A systematic review found that oral

midazolam was associated with a higher level of sedation and fewer adverse effects [71]. Additionally, oral midazolam has been shown to have a faster onset and shorter recovery time [71–73]. Intravenous sedation with propofol has also been found to be safe and effective in paediatric patients undergoing gastrointestinal endoscopy, and some studies even suggested it as the most effective in this context [74–79]. A study comparing propofol/fentanyl to midazolam/ketamine found that greater comfort was noticed among children undergoing sedation with midazolam/ketamine for upper gastrointestinal sedation than in the propofol/fentanyl group. However, ketamine adverse events were noticed in this group and should be considered in the evaluation of the overall effectiveness [80]. The choice of sedative should be tailored to the individual patient and the specific procedure being performed [81–83]. It is worth mentioning that the use of sedation should always be performed by a trained professional, and the use of monitoring devices should be considered to ensure patient safety [84, 85].

The elderly

There is limited evidence regarding sedation outcomes during endoscopy in the elderly population, although such procedures are commonly conducted. It is important to note that elderly patients may have an increased risk of adverse effects from sedation due to the changes in pharmacokinetics and pharmacodynamics that come with age. Moreover, lipophilic drugs usually have an increased half-life, which increases the risk of developing adverse events due to reduced hepatic and renal functions [86]. The presence of coronary artery disease and hypertension are other contributing factors that might deteriorate the kidneys' necessary metabolic and excretory functions [87]. Therefore, it is crucial to consider the patient's comorbidities and medications when choosing the appropriate sedative agent and dosage. Monitoring vital signs, including blood pressure, oxygen saturation, and heart rate, is also essential during sedation, to ensure patient safety [4].

Based on the aforementioned factors, midazolam might be a good choice for the elderly because the activity of CYP3A4 does not usually differ between young and old individuals [88]. The best practice of sedation can be done by lowering the dose and administering fewer agents at a slower rate. Moreover,

it has been suggested that tolerance to midazolam with old age might mitigate the risk of developing adverse events in the same population [89–91]. This has been indicated in a randomized controlled trial, which showed that good tolerance was more achievable by administering 30 µg/kg than when giving a placebo in a group of patients undergoing upper gastrointestinal endoscopy [92]. It should be noted that the intervention group also had an increased risk of hypoxaemia but not confusion and with no clinically-apparent hypotension.

Adjusting the dose for the elderly population is also important. For instance, a study demonstrated that the mean propofol dose needed for sedation for endoscopy was significantly lower for elderly adults than for younger patients [93]. The authors also demonstrated that no significant differences in the rates of adverse events were estimated between the 2 groups. Among elderly patients with various morbidities, it should be anticipated that propofol might be more sensitive, and combined use of propofol and midazolam might be safer [93]. Optimizing the dose required for sedation might be difficult depending on various factors, such as the patient's condition and type of endoscopic procedure (Table III). A previous study suggested that safe doses of propofol for sedation during ERCP, colonoscopy, percutaneous gastrostomy, and upper gastrointestinal endoscopy might be 42, 46, 24, and 22 mg, respectively, for patients > 70 years old. Moreover, no significant differences were noted between the elderly population and younger individuals regarding propofol blood concentration and the level of sedation after drug administration [94].

Chronic liver disease

Patients with chronic liver diseases might be indicated for a therapeutic or diagnostic endoscopy procedure, which might even be emergent. As we previously mentioned, with the elderly, impaired liver functions can deteriorate the metabolism of various drugs and biliary excretion, including sedatives. Deteriorated hepatic functions reduce the availability and effectiveness of enzymes necessary for drug metabolism, like CYP450. Accordingly, liver functions should be assessed before the procedure, and adequate physical examination should be done to exclude encephalopathy. In many cases, sedation might not be required. However, it might be need-

Table III. Factors affecting the choice of sedation

Factor	Explanation
Patient factors	Age, weight, medical history, pre-existing conditions (e.g. cardiovascular disease, respiratory disease), allergies, pregnancy status, level of anxiety, level of cooperation
Procedure factors	Type of procedure (e.g. diagnostic, therapeutic, surgical), duration, invasiveness, the potential for pain, location of procedure (e.g. inpatient, outpatient)
Provider factors	Experience and expertise of the provider, availability of equipment and drugs, personal preferences and biases, regional practices and regulations
Facility factors	Resources and facilities for monitoring and resuscitation (e.g. equipment for airway management, resuscitation drugs), policies and protocols for sedation, availability of trained personnel
Financial factors	Cost of drugs and equipment, insurance coverage, reimbursement policies
Patient preference	Desire for pain control, fear of side effects, preference for conscious sedation or deep sedation

ed in some cases with acutely bleeding varices for ligation [95–97]. In these events, dose adjustment should be prioritized, and renal excreted medications should be administered [98, 99].

Evidence shows that propofol is usually preferred as a sedative agent for cirrhotic patients. On the other hand, opioids and benzodiazepines are not preferred because of the high risk of inducing encephalopathy and the shorter plasma half-life. A previous study of 210 cirrhotic patients undergoing upper gastrointestinal endoscopy compared propofol plus fentanyl versus midazolam plus fentanyl, with administered doses of 50 µg (intravenous), 0.05 mg/kg, and 0.25 mg/kg of fentanyl, midazolam, and propofol, respectively. It was concluded that recovery time and safety were better in the group that was administered propofol, indicating its effectiveness and safety [37]. Precipitating overt or minimal hepatic encephalopathy does not usually occur with propofol administration in cirrhotic patients undergoing upper gastrointestinal endoscopy [100–102]. Another study further indicated propofol's effectiveness in reducing discharge and recovery time compared to midazolam in patients with compensated cirrhosis [103]. Accordingly, it can be concluded that propofol is safe and effective for sedating patients with chronic liver diseases.

Obesity

The number and burdens of obesity are steadily increasing worldwide. Accordingly, the number of endoscopic procedures is also increasing [104, 105]. However, data regarding sedation practices for endoscopic procedures in obese individuals are not adequate to make conclusions about the safety

and efficacy of these approaches. Therefore, sedating such patients should be carefully approached to intervene against the development of unexpected events [106, 107]. Some studies investigated the efficacy and safety of sedation for obese patients undergoing upper gastrointestinal endoscopy and other advanced endoscopic procedures for bariatric surgeries. For instance, a study reported a mean dose of 380 mg of propofol for successfully sedating their population of 69 obese patients undergoing upper gastrointestinal endoscopies amid bariatric surgeries. The authors further reported no adverse events except for 2 patients who suffered from severe hypoxaemia. However, they were effectively managed by bronchoscopic intratracheal O₂ insufflation [108]. Accordingly, adequate perioperative monitoring is required, particularly for patients with comorbid conditions.

Another investigation demonstrated that increased body mass index was a significant risk factor for hypoxaemia and airway manoeuvres among individuals undergoing sedation with propofol for different endoscopic procedures. A multivariate analysis was also conducted and showed that the development of complications could be significantly predicted by body mass index. However, it should be noted that the rates of reported complications did not differ between obese patients receiving propofol alone or in combination with other sedatives [109]. Another factor to be considered is the difference in the rates of complications between surgeon- or anaesthesiologist-monitored sedation. A previous study demonstrated that both approaches are safe and effective. However, minor adverse events are significantly lower with anaesthesiologists, which

might favour their use for advanced upper gastrointestinal endoscopic procedures [110].

Others

There are other situations where additional care is required to maximize the safety and efficacy of sedation for digestive endoscopic procedures. For instance, some sedative considerations should also be made for patients with coeliac disease, who are at increased risk of visceral hypersensitivity and neuropsychiatric disorders [111]. A previous retrospective investigation demonstrated that higher amounts of midazolam and opioids were required in 26% of patients with coeliac disease compared to their matched controls [112]. This has been attributed to the underlying neuropsychiatric conditions in these patients, chronic anxiolytic/opioid use, and increased visceral hypersensitivity.

Moreover, additional care might be needed in cases of advanced digestive endoscopic procedures, which might require prolonged periods of sedation. Some of these procedures might include endoscopic mucosal dissection (ESD), endoscopic ultrasonography, and ERCP. These procedures usually take longer than conventional ones, requiring deeper sedation and more advanced care to enhance sedation practices and intervention against potential complications. Various studies have been published in this context to evaluate the safety and efficacy of sedation practices and dosages, and to compare the effectiveness of combined versus single-drug administration [113–115]. For instance, a previous study showed that the efficacy of ESD for early gastric cancer was comparable between intermittent midazolam injection and continuous propofol infusion [116]. However, it has been shown that a faster recovery period was noted among patients sedated with propofol. The authors also indicated the efficacy and safety of propofol and midazolam in this context [116]. It should be noted that this was also reported and validated for the sedation of patients undergoing ESD [117–119]. The dosage of this drug was reported as an intravenous dose of 3.0 µg/kg/h over 5 min, followed by continuous infusion at 0.4 µg/kg/h [120]. This was reported in a randomized trial, which also showed that the efficacy of this modality was significantly higher than that of midazolam and propofol. Moreover, reduced O₂ saturation levels were not observed among any of the included patients receiving dexmedetomidine.

Accordingly, sedation with dexmedetomidine was deemed safe and effective for ESD [4]. Wang *et al.* [121] also investigated the effectiveness and safety of Enhanced Recovery After Surgery (ERAS) protocols in patients having peroral endoscopic myotomy (POEM), compared to a conventional group. Preoperative education, fasting time before surgery, temperature control during surgery, fluid management, and pain relief were all addressed in the ERAS protocol. The findings indicated that ERAS was associated with a higher quality of recovery-15 (QoR-15) score, lower VAS, and earlier resumption of oral feeding and readiness for discharge than conventional care. Accordingly, applying ERAS for these operations is more effective and safer, and it is usually associated with enhanced rates of patient satisfaction.

Regarding ERCP, a previous study compared safety profiles, recovery scores, and satisfaction between continuous propofol infusion and conventional sedation with intermittent meperidine and midazolam for patients undergoing ERCP. The authors demonstrated that the reported outcomes for both groups were not significantly different, except for the recovery rate, which was better in the continuous propofol group [122]. Moreover, it is well-established that propofol administration is much safer when used in diluted form. This has been investigated in a previous study of patients undergoing ERCP, which showed that the requirements were not different between both groups. The incidence of sedation-related hypotension was higher in the undiluted propofol group [123].

Another investigation also indicated that patient-controlled sedation for ERCP with remifentanyl/propofol is associated with good outcomes. The authors also demonstrated that deep sedation for ERCP can be significantly obtained by continuous propofol infusion without any adverse impacts on gastroenterologist satisfaction or patient degree [124]. It should be noted that conscious sedation can be safely and effectively done for ERCP and endoscopic ultrasound within the same day. However, conducting combined procedures increases the risk of prolonged recovery time and increased doses of sedation [125]. Another study also demonstrated that reducing the dose of propofol infusion for ERCP sedation can be done by administration of a 7.5 mg dose of midazolam 30 min before the infusion [126]. A higher level of satisfaction, due to favourable effectiveness and safety, for endoscopists and

patients undergoing endoscopic ultrasonography was also reported in a previous clinical trial for patient-controlled sedation with combined propofol and fentanyl than with pethidine and midazolam [127]. Another randomized controlled trial by Koruk *et al.* [128] compared the efficacy of propofol (used as maintenance) with midazolam (preoperative 0.05 mg/kg 10 min) versus propofol (used as maintenance) with dexmedetomidine (1 µg/kg for 10 min) in patients undergoing ERCP. The authors concluded that recovery time and propofol consumption were significantly shorter in the dexmedetomidine group compared to the midazolam group (time to achieve the Aldrete score 9 was 9.4 ± 2.1 vs. 6.6 ± 1.1 min, $p < 0.001$; 208.5 ± 80.0 vs. 154.5 ± 66.7 mg, $p = 0.011$). Moreover, both groups had comparable sedative and adverse events, indicating the safety and efficacy of dexmedetomidine, which can be used as an alternative sedative in these procedures.

Costs and economic issues

Effective sedation during digestive endoscopies can significantly decrease patient anxiety and discomfort, facilitating the procedure by increasing patient cooperation. The increased satisfaction scores reflect this among patients based on their perceived quality and readiness to undergo another procedure whenever needed. It has been furtherly demonstrated that such effectiveness is usually associated with increased surgical, scientific, and clinical quality based on gastroenterologists' perspective because they can better perform upper and lower exploration procedures, which have been associated with improved adenoma resection rates and enhanced main quality indices [129–133]. However, besides the issues mentioned above, the effectiveness of sedation during digestive endoscopies might also be burdened by financial costs. The financial burden of sedation is represented by fungible (O₂ administration devices, drip systems, venous access catheters, and others), non-fungible material costs (monitoring equipment), and pharmacological costs (intravenous fluids and drugs), together with other perioperative procedures that are necessary for patient evaluation. Moreover, the impact of sedation on the length of the procedure might be another factor to consider. This is because sedation for endoscopy usually requires extra time for induction of sedation and previous venous access cannulation. Additionally,

the perioperative of patients until recovery and discharge following endoscopy might be an additional factor affecting the efficiency of this approach [5]. Moreover, sedation in these events usually requires training and the presence of other trained professionals, such as anaesthesiologists, for patient monitoring and safety during the procedure. Therefore, proper planning of the sedation and analysing these factors should be approached to enhance the efficiency of these procedures [5].

Quantifying the economic burden and efficiency of sedation for endoscopic procedures remains challenging. Because patient outcomes, degree of satisfaction, and safety are important parameters for the overall quality of such procedures, it is difficult to assess the cost-effectiveness of these events. However, it should be noted that such a burden is usually variable among different centres and countries and can be influenced by many factors, including the rate and time of recovery and hospitalization per the actual population indicated for sedation, and population characteristics, such as age and the presence of comorbidities [134]. For instance, heavily occupied centres usually prefer procedures with reduced recovery and induction times. On the other hand, centres with lower rates are not usually burdened by the prolonged hospitalization time of patients. Therefore, these factors might not be important in determining the efficiency of sedation in these centres [135, 136].

Choosing the most appropriate drug is also important to consider when assessing the efficiency of sedation. For instance, among benzodiazepines, using midazolam is preferred because of its short half-life and rapid onset, providing more rapid induction of sedation and faster recovery compared to other sedatives within the same class [137]. Among opioids, it has been demonstrated that shorter recovery time and shorter inductions can be obtained with fentanyl more significantly than meperidine [138–141]. Shortening the induction and recovery time significantly enhances the efficiency of the sedation and endoscopy units. It has been further shown that these times are even more significantly shorter with propofol than benzodiazepines and opioids for sedation of advanced and basic endoscopic procedures [18, 142]. Moreover, previous studies have even concluded that these times are significantly better with propofol-induced sedation by a non-anaesthetist compared to benzodiazepines and opiates. Another study showed that anaesthesiologist-administered

propofol sedation is not cost-effective when conducted for routine endoscopic procedures for low-risk, healthy individuals [25, 142, 143]. However, it should be noted that choosing a sedation-induction strategy over the other should be based on careful balancing between different parameters, including quality of care and outcomes, satisfaction, and costs.

Legal issues

Various legal issues have been raised in the literature for the practice of sedation. These are mostly related to issues regarding monitoring according to accepted standards and protocols, consent from sedation patients, and use of propofol by the personnel conducting the sedation [144–146]. Dispensing in the presence of an anaesthesiologist (i.e. conducting sedation by a non-anaesthesiologist) should only be done with optimal characteristics of the sedative, like minimal associated risks and low profile of adverse events, short recovery time, potent anxiolytic/analgesic effects, and a predictable pharmacokinetic profile. It should be noted that some studies also validated the safety of practicing sedation by non-anaesthesiologists with drugs like propofol [15, 147]. Further studies also demonstrated the safety and efficacy of propofol-related sedation conducted by physicians and trained nurses for upper gastrointestinal endoscopic procedures [127, 148–150]. Evidence from these studies indicates no deaths in cases requiring endotracheal intubation. Moreover, a trial of 36,743 nurse-conducted propofol sedations showed that adequately trained endoscopists and nurses could safely and effectively conduct propofol sedation [33]. The impact of endoscopists' direction over sedation was indicated by Rex *et al.* [25] because 11 cases had endotracheal intubation, and 4 cases, among a total population of 646,080, died following propofol-administered sedation. A multi-country survey should that 29.9% of the participants from 9 countries had propofol sedation by a non-anaesthesiologist for colonoscopy. Moreover, around two-thirds of other participants reported that non-anaesthesiologist administered propofol sedation could be conducted for low-risk patients [151]. The reasons for not conducting sedation by non-anaesthesiologists were mainly related to costs and medico-legal issues [4].

It should be noted that most of the reported complications during digestive endoscopy are due to sedation and not the endoscopic procedure itself.

Therefore, optimizing the quality of sedation in these events is important. A previous trial demonstrated that patient levels of satisfaction and willingness to undergo sedation under the same conditions were better for patients undergoing endoscopist-administered sedation than for those undergoing anaesthesiologist-administered sedations [152]. Conducting sedation by non-anaesthesiologists remains controversial. According to the American Society of Anesthesiologists and the Royal College of Anaesthetists, ideal propofol sedation should be conducted by anaesthesiologists and the Royal College of Anaesthetists. On the other hand, the guidelines of the Endoscopic Section of the German Society for Digestive and Metabolic Diseases suggest that anaesthesiologists should be involved in high-risk sedation, and propofol sedation can be effectively and safely conducted if adequately trained personnel are involved. Similar suggestions were also found in other worldwide guidelines [4, 28]. It should be noted that almost all these societies recommend against non-anaesthesiologist administered propofol sedation. Overcoming different obstacles, like providing anaesthesiologists for sedation in endoscopies, staffing, and funding, remains challenging [28].

Conclusions

Sedation is an essential component of digestive endoscopy. It not only improves patients' comfort but also allows the endoscopist to perform the procedure efficiently and accurately. However, using sedation in endoscopy poses several challenges, including the risk of adverse events and the need to monitor patients during and after the procedure. One of the most significant recent issues in sedation for digestive endoscopy is the increasing use of propofol, which has replaced traditional sedatives such as midazolam. Propofol has been associated with a higher risk of adverse events, including respiratory depression and cardiac arrest. Therefore, it is crucial to monitor patients receiving propofol properly and have proper resuscitation equipment readily available in an emergency. Another issue is the need for trained personnel to administer sedation and monitor patients during the procedure. The shortage of trained anaesthesiologists has led to the use of non-anaesthesiology personnel, including endoscopists, to administer sedation. However, this practice has raised concerns about patient safety

and the need for proper training and certification of personnel administering sedation. Further research is needed to evaluate the optimal sedation administration and patient monitoring methods and develop guidelines to ensure the safe use of sedation in digestive endoscopy.

Conflict of interest

The authors declare no conflict of interest.

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