Analgosedation and Periprocedural Care for Gastrointestinal Endoscopy

Subjects: Anesthesiology

Contributor: Sonja Skiljic , Dino Budrovac , Ana Cicvaric , Nenad Neskovic , Slavica Kvolik

The number and complexity of endoscopic gastrointestinal diagnostic and therapeutic procedures is globally increasing. Procedural analgosedation during gastrointestinal endoscopic procedures has become the gold standard of gastrointestinal endoscopies. Patient satisfaction and safety are important for the quality of the technique. The ideal analgosedation technique should enable the satisfaction of the patient, their maximum safety and, at the same time, cost-effectiveness. Although propofol is the gold standard and the most used general anesthetic for endoscopies, its use is not without risks such as pain at the injection site, respiratory depression, and hypotension. New studies are looking for alternatives to propofol, and drugs like remimazolam and ciprofol are in the focus of researchers' interest. New monitoring techniques are also associated with them. The optimal technique of analgosedation should provide good analgesia and sedation, fast recovery, comfort for the endoscopist, patients' safety, and will have financial benefits. The future will show whether these new drugs have succeeded in these goals.

endoscopy gastrointestinal conscious sedation monitoring anesthesia

1. Type of Endoscopic Procedures and Analgosedation Procedures

In addition to relatively simple, short-term gastroscopies and colonoscopies, more complex endoscopies of the digestive tract with different diagnostic and therapeutic goals are also performed. These procedures include esophagogastroduodenoscopy (EGD) [1], endoscopic ultrasound (EUS), therapeutic endoscopic ultrasound (TEUS) [2], enteroscopy [3], percutaneous endoscopic gastrotomy [4], endoscopic removal of neoplasms, endoscopic retrograde cholangiopancreatography (ERCP) [5], and removal of foreign bodies from the GI system in children or adult patients [6][7]. The increasing role of artificial intelligence in the fields of GI endoscopic examinations such as video-capsule-endoscopy will, in the near future, enable a high level of complexity of these examinations [8]. The complexity of endoscopic examinations is determined by the urgency and duration of the procedure, as well as the general condition, age, and comorbidities of the patients undergoing it. More complex and longer endoscopic procedures are associated with greater patient discomfort and pain.

Most gastroscopies and colonoscopies are performed as part of routine screening programs. For these procedures, light to moderate analgosedation with monitoring based on clinical assessment of the level of sedation and basic vital parameters is sufficient. More complex endoscopic procedures require general anesthesia with appropriate protection of the airway, endotracheal intubation, and objective monitoring of vital parameters. In addition to the endoscopic technique itself, associated comorbidities in high-risk patients may require general anesthesia. Such conditions are obstructive sleep apnea, morbidly obese patients, procedures in patients with dementia or cognitive impairments, procedures in children, in patients with an estimated difficult airway maintenance, and various cardiorespiratory diseases.

Emergency conditions, such as active bleeding from the digestive tract with a high risk of aspiration of gastric contents, impose the need for general anesthesia and airway protection [9]. In such cases, there is an unquestionable need for educated anesthesiology staff, equipment, and objective monitoring, often with additional laboratory tests. In the case of cardiovascular and respiratory instability of a patient under general anesthesia, in addition to clinical assessment of analgosedation, electrocardiography, pulse oximetry, capnography/capnometry, and non-invasive measurement of blood pressure, there is often a need for extended monitoring. It consists of continuous measurement of systemic arterial pressure, acid-base status, and objective monitoring of the depth of sedation using the bispectral index (BIS) or entropy [10].

Preoperative laboratory tests should not be performed routinely. For healthy patients undergoing routine diagnostic endoscopies with normal clinical status, and who do not take any medication, no laboratory tests are necessary in preparation for anesthesia [11]. For at-risk patients, indicated laboratory tests may be selectively requested after clinical examination and history. Their goal is to correct the disorder and achieve the optimal condition of the patient before the planned anesthesia. Hemoglobin will be determined in patients with a history of anemia, the elderly, patients with a bleeding disorder, or with hematological diseases [11]. Coagulation tests will be requested before a planned endoscopy under anesthesia if the patient has a known clotting disorder, liver, or kidney dysfunction, or is taking anticoagulant therapy. This is especially important when biopsies or endoscopic resection of intraluminal polyps are planned [11].

2. The Level of Education of Personnel Performing Sedation Techniques in Gastrointestinal Endoscopy Practice

Procedural short-term analgosedation during gastrointestinal endoscopic interventions relieves patients' discomfort, allowing mild muscle relaxation. Procedural sedation has become the gold standard and is a condition without which these procedures cannot be easily performed. Patient satisfaction with this service is an indicator of the overall quality of the medical service provided in healthcare institutions. Most endoscopies are short-term, outpatient, minimally invasive procedures after which the patient soon leaves the healthcare facility. The role of periprocedural analgosedation in this setting is to eliminate the anxiety, discomfort, and stress that the patient currently feels, and to ensure relaxation of skeletal muscles, thereby improving the performance of endoscopy, without affecting vital functions. Because of this, periprocedural analgosedation is widely accepted by both patients and endoscopists.

Dossa and colleagues performed literature searches of articles published from 2005 to 2019. They have identified 19 different guidelines and seven recommendations for analgosedation techniques for performing endoscopic gastrointestinal examinations, which include the choice of different sedation drugs, the type of competent health personnel, and appropriate monitoring. Based on these results, they concluded that the existing recommendations and guidelines vary significantly depending on the countries and professional societies that issued them and that most of them are not based on strong scientific evidence [12]. Sedation techniques, the selection of drugs, monitoring, and the degree of specific education of the professional staff who provide the service during gastroenterology endoscopic examinations, differ between continents and countries around the world. In some European and Asian countries, specially trained nurses and gastroenterologists are the ones who provide sedation for endoscopic gastroenterological procedures. According to the meta-analysis by Dossa et al., the personnel providing light to moderate sedation may be educated nurses, as well as the endoscopist themselves, while it is recommended by most professional gastroenterology societies that analgosedation for complicated patients should be performed by an anesthesiologist [12].

Most sedation procedures require an available anesthesiology team to be available for the needs of emergency intervention, especially related to the compromised airway. Besides, some parts of the world suffer from a lack of highly educated anesthesiologic staff for short-term sedation during the performance of a large number of such examinations on a daily basis. Such a procedure is, for example, a routine or screening colonoscopy. Therefore, the cost–benefit ratio of anesthesiologic engagement for this purpose is often questioned. In contrast to the costs, patient safety must be guaranteed and is a fundamental condition of every medical service provided in controlled medical conditions according to the principle of "*primum non nocere*". Important factors that influence the need for anesthesiologic presence are also the ASA status of the patient ASA ≥ III, Mallampati status ≥ three, the presence of anomalies/deformations of the face and airway, perioperative assessment of difficult intubation, and mask ventilation. Patients' comorbidities, non-cooperation, chronic opioid use, and duration and complexity of the endoscopic intervention itself further complicate the decision and require a detailed periprocedural assessment and triage of the patient by a specialized physician [12].

Due to all the above, there is still a lack of a unique, ideal anesthetic/sedative that would be of use in creating applicable guidelines. An ideal sedative should have quick and simple administration, rapid onset of action, achieve anxiolysis and light to moderate sedation, possible amnesia, have desirable pharmacokinetic and pharmacodynamic properties, and enable the performance of gastroenterological procedures for ambulatory patients. At the same time, it should be free of unwanted effects on the respiratory and cardiovascular systems, and should have rapid elimination, and cessation of action after discontinuation of use, with no or negligible residual effect and rebound phenomenon. For this purpose, numerous anesthetics, sedatives, and opioid and non-opioid analgesics have been used over the years, as well as various adjuvant drugs that are mostly used in everyday anesthesiology practice.

3. Old and Novel Sedation Techniques for Gastrointestinal Endoscopies

Among the most used traditional drugs for sedation in gastroenterology practice are benzodiazepines in combination with opioids [13]. For example, in Great Britain, over 2.5 million endoscopic interventions are performed annually under the sedation effect of benzodiazepines and opioids, mostly prescribed by the endoscopists themselves [9]. Among benzodiazepines, the use of midazolam prevails. Midazolam is a well-studied benzodiazepine class sedative/anesthetic agent with antero-grade amnesic properties. It can be administered in combination with other drugs, especially opioids which potentiate its sedative and analgetic properties. It is preferred over other benzodiazepines because of its pharmacokinetic profile with rapid effects after and short duration of action, which makes it the favorite choice of sedation in short, non-surgical procedures, and outpatient examinations. A meta-analysis of studies comparing the effects of midazolam versus the newer remimazolam confirmed that more rescue drugs were used with midazolam, with a higher frequency of side effects, especially hypotension [14]. Remimazolam, according to current knowledge, might be a quality substitute for midazolam.

Propofol is currently the backbone of sedation in gastroenterological interventions and the most used intravenous anesthetic in clinical practice for procedural sedation, alone or in combination with opioids [15]. Propofol is characterized by rapid onset and cessation of action and high extra-hepatic clearance [16]. Due to its characteristics, it is suitable both for induction to general anesthesia but also for sedation for endoscopic procedures [17]. In subanesthetic doses, it leads to sedation and anxiolysis, the effect of which is dose-dependent. Despite its many advantages, it also has certain disadvantages. Propofol has a narrow therapeutic window and is characterized by dose-dependent cardiovascular and respiratory depression, especially in frail and elderly patients [18].

Remimazolam tosilate (HR7056, RT) is a new, short-acting benzodiazepine developed in China. The drug is broken down by plasmatic tissue esterases into inactive metabolites. It is an ultra-short-acting sedative with a predictable time effect, which makes it preferable for short-term procedural sedation. As of 2020, it has been approved as a short-acting sedative and intravenous anesthetic in China, South Korea, Japan, Europe, and the USA [19].

Remifentanil should be highlighted due to its unique metabolic pathway compared to other opioids. It therefore has a short-acting analgesic effect desirable for endoscopic procedures in gastroenterology. Although it does not differ pharmacodynamically from other opioids, its rapid elimination through plasma cholinesterase makes it suitable for patients with impaired liver function, which is common in gastroenterology patients [13]. The clinical effect of sedation is achieved with a bolus dose that is continued by titrating a continuous infusion depending on the patient's weight (0.4–0.6 μg/kg/min). This may be a drawback in the practicality of drug administration and requires additional equipment. Remifentanil is used in clinical practice as an adjunct in combination with sedatives/anesthetics such as propofol, ketamine, hypnomidate, and midazolam [20][21][22].

Oliceridin is a newer drug from the opioid group, that activates G-protein signaling, with exceptional selectivity for μ-receptors [23]. Classical opioids such as fentanyl act on μ-opioid receptors, which are responsible for the analgesic effect, but in the sequence of activation they also act on β-arrestin receptors. These receptors are thought to be responsible for unwanted effects such as respiratory depression and gastrointestinal side effects. Oliceridine is a μ-opioid agonist that has only 14% of the β-arrestin activity compared to morphine. It was approved by the FDA in 2020 for the treatment of moderate and severe acute pain [24]. No dose adjustment of oliceridine is necessary for patients with renal impairment or for patients with mild to moderate hepatic impairment. Dose reduction is necessary in severe renal impairment [25].

Dexmedetomidine is a sedative drug, a short-acting highly selective alpha-2 receptor agonist. It has an analgosedative effect, while preserving alertness, airway patency, protective reflexes, and spontaneous breathing. It is approved for sedation in intensive care units. During the administration of dexmedetomidine, the patient is in a state known as “conscious sedation”, which theoretically makes it the ideal choice of sedative for the needs of gastroenterological procedures. Among the unwanted side effects are the impracticality of drug administration in continuous infusion, and the possibility of severe hypotension and bradycardia associated with fast intravenous administration. In their meta-analysis comparing propofol and dexmedetomidine for achieving sedation during gastrointestinal endoscopies, Nishizawa et al. concluded that there was no difference in adverse cardiorespiratory events between propofol and dexmedetomidine, but that patient satisfaction in the propofol group was significantly higher compared to dexmedetomidine [26].

Fospropofol (2,6-diisopropylphenoxymethyl phosphate disodium salt) is a possible alternative to propofol, and unlike propofol, it is water-soluble. Fospropofol is a prodrug of propofol that is hydrolyzed on the surface of endothelial cells into propofol, and into phosphate and formaldehyde. Formaldehyde is then metabolized in the liver and in erythrocytes [27]. Clinical studies have not reported toxic concentrations of formaldehyde in serum that would lead to metabolic acidosis, vision loss, and death [27][28]. Its application is not as painful as with propofol, and the risk of bacterial contamination and hypertriglyceridemia is lower [29]. The pharmacokinetics of fospropofol takes place through a two-compartment model, in contrast to propofol, whose kinetics is observed through a three-compartment model [27].

Ciprofol is a newer intravenous anesthetic, a propofol derivative presented to the market as a promising alternative. Its chemical structure is very similar to propofol, so it has similar pharmacodynamic and pharmacokinetic properties. It is characterized by rapid onset of action, rapid recovery, and high clearance [30].

4. Monitored Anesthesia Care for Gastrointestinal Endoscopy

The frequency and complexity of endoscopic GI diagnostic and therapeutic procedures are constantly increasing. The purpose of monitored anesthesia care (MAC) itself is to provide patients with comfort and, above all, pain control and safety. Considering that these procedures are unpleasant and painful for the patient, they are increasingly looking for different techniques of anesthesia or sedation [31][32][33]. A gastroenterologist who performs the procedure in this way can also improve the quality and efficiency of the examination itself, because the patient is cooperative, and the gastroenterologist can be focused on performing the endoscopy [33]. Preparation for MAC is very similar to that for general or regional anesthesia. The goal is to inform the patient about the entire planned procedure and progress, identify medical risks, and optimize the patient’s condition. During the preoperative evaluation, a physical examination should be performed, and the patient’s history should be taken, which includes information about the current problem, associated diseases, information about previous anesthetic procedures, current medications being taken, allergies and potential respiratory tract disorders. In patients who are at risk of malabsorption and malnutrition, the anesthesiologist should have insight into the results of relevant laboratory findings and associated tests. The most common complications in patients undergoing gastrointestinal endoscopic procedures are hypotension, aspiration, and hypoxemia [34]. The goal of the evaluation is to identify the patient's current condition and to create an anesthesia plan that minimizes risks.

New means of communication, such as smartphones with mobile applications, can help in early recognition of deterioration or recovery of a patient with GI diseases. A mobile application was created for patients with inflammatory bowel disease [35]. Patients filled out a questionnaire every day, and the data were processed in the electronic medical record. Based on their answers, alerts or red flags were created, which can be monitored. The central processing of these answers can indicate the urgency of a visit to the doctor or time in which it is possible to perform the planned endoscopy and reduce the scope of examinations. Their application can help in confirming disease remission, determining the patient's general condition, and the need for emergency or control endoscopy can be facilitated [35]. If they are at special risk, such patients will be referred to an anesthesiologist for endoscopy, and for patient safety, NAAP or other procedures performed by non-anesthesiologists should be avoided.

For MAC, similar drugs are used as for general anesthesia, in lower, sedation doses, to maintain spontaneous ventilation [36]. Therefore, continuous standard monitoring of the patient must be included (certainly ECG, non-invasive pressure measurement, and monitoring of oxygenation via a pulse oximeter) along with monitoring of the patient's airways and breathing [37][38].

BIS monitoring is a non-invasive method that processes EEG information, thus enabling measurement of the patient's level of consciousness and depth of sedation. By using BIS monitoring, it is possible to reduce the applied dose of the drug, and the risk of too deep sedation, especially in elderly patients [39][40][41][42]. Considering the great heterogeneity of the conducted studies related to the use of BIS monitoring, other studies did not establish a specific clinical benefit that would include more adequate and improved oxygenation of patients, and a reduction in the risk of respiratory and circulatory complications [43][44][45].

After a gastrointestinal diagnostic or therapeutic procedure, the patient should be awake and oriented, with no signs of complications. The patient should be monitored after the procedure in the recovery or post-anesthesia care unit, where any problems that may develop can be quickly recognized and treated. Signs of a good recovery are full alertness, spontaneous breathing without oxygenation in room air, and hemodynamic stability. Safe discharge can be planned for these patients [46].

Due to all the above, and due to the recognition of adverse events, the presence of an anesthesiologist during sedation for gastrointestinal procedures is recognized as useful, as it reduces the possibility of unwanted consequences, improves patient satisfaction, and improves the patient's post-procedural recovery [46][47].

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