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Sedation during endoscopic procedures: a Hellenic Society of Gastroenterology Position Statement

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Abstract

Administration of sedation by non-anesthesiologists during gastrointestinal endoscopy remains highly controversial in Greece. The aim of this set of 16 position statements prepared by experts in the field on behalf of the Hellenic Society of Gastroenterology is to aid gastroenterologists in their everyday clinical practice and provide evidence for the best use of drugs for the sedation of patients who undergo an endoscopy. The statements address issues such as the level of sedation required, the best drugs used, their mode of action, their side-effects and possible ways to counter their action, and were adopted if at least 80% of all participants agreed upon them.

Keywords Sedation, gastrointestinal endoscopy, propofol, Hellenic Society of Gastroenterology, Consensus

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Introduction

Although esophagogastroduodenoscopy and colonoscopy can be performed without sedation, both procedures are better tolerated when sedation is administered [1]. Sedation may be defined as a drug-induced depression of the patient's awareness of the environment, and reduction of his or her responsiveness to external stimulation [2]. In gastrointestinal endoscopy, sedation is intended primarily to reduce patients' anxiety and stress before endoscopy, as well as the pain and discomfort associated with the procedure. Improving the acceptability of the procedure can lead to earlier detection of malignant lesions and other diseases of the gastrointestinal tract [3]. Endoscopic sedation also minimizes the patient's risk of physical injury during an examination, providing the endoscopist with an ideal environment for a thorough examination [4]. Sedation comprises a continuum of states ranging from minimal (anxiolysis) through general anesthesia [5] (Table 1).

Practice guidelines for non-anesthesiologists providing sedation have been published by the American Society of Gastrointestinal Endoscopy (ASGE) [5], the European Society of Gastrointestinal Endoscopy (ESGE), European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology [1] as well as the Japanese Gastroenterological Endoscopy Society, and the Japanese Society of Anesthesiologists [6]. However, guidelines for Greek gastroenterologists and physicians performing endoscopic procedures are lacking. Towards this end, the Hellenic Society of Gastroenterology organized a meeting to

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provide medical doctors who participate in gastrointestinal endoscopy and are not anesthesiologists with a comprehensive framework on how to implement sedation in their everyday clinical practice in Greece. The aim of this publication is therefore to report these statements in order to aid the local gastrointestinal community in their endoscopy practice.

Methodology

Fifty-six gastroenterologists from all Hellenic regions took part in the position statement meeting. All 56 gastroenterologists were nominated by the President of the Hellenic society of Gastroenterology; they were skilled endoscopists, working in public or private hospitals and having many years of endoscopic experience, while all of them have served in the governing board of either the main Hellenic Society of Gastroenterology or its endoscopic section. The participants were divided into 16 groups and each group had to answer a specific question regarding sedation during endoscopic procedures, giving a short statement followed by the relevant justification and references. The questions were specifically chosen to address issues such as the level of sedation required, the best drugs used, their mode of action, their side-effects, and possible ways to counter their action. The questions were divided into 7 sections: i) preparation for sedation; ii) monitoring of the patient and equipment needed for the administration of sedation; iii) training of the endoscopists who administer sedation; iv) drugs used for sedation: sedatives and analgesics; v) the use of propofol; vi) the presence of an anesthesiologist; and vii) sedation antagonists – endoscopy report. Although most of these issues have already been addressed in previously published guidelines by the European [1], American [5], and Japanese [6] endoscopic societies, the current position statement aims to express the point of view of the Greek Society of Gastroenterology, since there was previously no consensus between the Greek Gastroenterology and Anesthesiology Societies.

Table 1 Levels of sedation

Level of sedation	Characteristics
Minimal sedation	Equivalent to anxiolysis, i.e., drug-induced relief of apprehension with minimal effect on sensorium. Airway reflexes, spontaneous ventilation and cardiovascular function remain unaffected
Moderate sedation	Depression of consciousness in which the patient can respond to external stimuli (verbal or tactile). Airway reflexes, spontaneous ventilation, and cardiovascular function are maintained
Deep sedation	Depression of consciousness in which the patient cannot be aroused, but responds purposefully to repeated or painful stimuli. The patient may not be able to maintain airway reflexes or spontaneous ventilation, but cardiovascular function is preserved
General anesthesia	State of unconsciousness: the automatic nervous system is unable to respond to surgical or procedural stimuli. Airway reflexes often require intervention, spontaneous ventilation is frequently inadequate and cardiovascular function may be impaired

Each group performed a literature search in PubMed, Embase and the Cochrane Library databases using 2 main terms, "sedation" and "gastrointestinal endoscopy", and additional term(s) pertaining to its own topic. The search identified studies published as full papers in English from 2000-2021. In particular, the search focused on prospective studies (especially randomized controlled trials) and meta-analyses. Retrospective studies could be considered if they addressed topics not covered in the prospective studies.

Each group had a coordinator, responsible for presenting the group's statement at a meeting organized by the Hellenic Society of Gastroenterology. At this meeting the coordinator presented his group's statement, while each presentation was followed by extensive discussion, with modifications, additions and deletions. The conclusions and recommendations for each group were then edited and presented to all participants for the final voting. Each statement was adopted if at least 80% of all participants agreed upon it. If <80% of participants agreed on a statement, then the statement was revised, and participants were asked to vote again (up to 3 total voting rounds) [7]. The number of voting rounds needed to reach 80% of agreement is also presented for every statement. The questions, together with the relevant statements as well as the levels of agreement from these proceedings, are presented in this paper. A short justification, with the evidence that led to each statement, can also be found in the text. All statements are summarized in Table 2.

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Table 2 Summary of statements

Statement	Summary
1	Safe sedation during endoscopic procedures requires the determination of the level of sedation and the general performance status of the patient, as assessed by medical history, detailed physical examination and the international classifications
2	Informed signed consent for the administration of sedation is necessary and should be obtained by the physician who will perform the endoscopy
3	Appropriate monitoring of the sedated patient during endoscopy should include clinical evaluation of their level of consciousness and monitoring of cardiorespiratory function and hemodynamic stability
4	The monitoring of the sedated patient ends when the basic level of consciousness has been recovered and the patient is no longer at risk for cardiorespiratory depression
5	The minimum equipment required for the administration of mild-to-moderate sedation includes a pulse oximeter, an O_2 supply source, a suction device and the appropriate airway patency equipment. For deep sedation anesthesiological support is needed
6	Sedation during endoscopy is administered by sufficiently trained physicians and non-physician ancillary personnel, who should undergo constant training
7	Apart from local anesthetics, during endoscopic procedures patients receive sedatives (such as benzodiazepines and propofol) and/or analgesics (such as opioids) in titrated doses, in order to achieve the desired level of consciousness, depending on the type of the procedure, and the patient's age and general medical status
8	The benzodiazepines that are mainly recommended for sedation during endoscopy are primarily midazolam and alternatively diazepam both administered intravenously
9	The use of analgesics in combination with sedatives, especially for endoscopies anticipated to cause higher levels of pain and discomfort or to have longer duration, reduce the patient's discomfort and pain, and increase endoscopist comfort
10	The use of propofol is superior to the classical sedation drugs during interventional endoscopic procedures because the patient's satisfaction is greater and the recovery time is shorter
11	Propofol can be administered by properly trained gastroenterologists, in endoscopy rooms well equipped and in patients with ASA score I-II
12	If the above requirements are not met and/or in patients with ASA score >III an anesthesiologist should be present
13	Sedated endoscopy examinations can be safely conducted on patients with special conditions or chronic diseases, provided that the endoscopist evaluates both the patient's ASA status and the complexity of the endoscopic procedure in order to provide mild-to-moderate sedation
14	During urgent endoscopy in severely ill patients whose cardiorespiratory function is compromised, assistance from an anesthesiologist is recommended. In the remaining cases, the recommended sedation is via titrated administration of a sedative with a relatively short half-life and an action that is or is not reversible
15	The administration of sedation antagonists for the reversal of sedation is recommended for patients with respiratory suppression unresponsive to verbal commands
16	The medication administered including dosage, the vital signs and events (if any) during and after the procedure and the patient's full recovery before discharge from the endoscopic unit should be reported

ASA, American Society of Anesthesiologists

Questions and Statements

Section 1: Preparation for sedation

What should pre-sedative patient assessment include during endoscopic procedures?

Statement 1: Safe sedation during endoscopic procedures requires the determination of the level of sedation and the general performance status of the patient as assessed by medical history, detailed physical examination and the international classifications

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***94%***

Safe sedation during endoscopic procedures requires the determination of the level of sedation, the general performance status and the medical history of the patient, especially any previous adverse reaction to sedation. In addition, the clinical history should note any serious cardiopulmonary conditions, sleep apnea, drug allergies, and tobacco, alcohol and drug consumption, as well as pregnancy and lactation, in view of the teratogenic effect of some sedatives [8].

A focused physical examination should include vital signs, heart and lung auscultation, assessment of general performance status according to the American Society of Anesthesiologists (ASA) classification (Table 3) [9], consciousness level and airway assessment according to Mallampati's classification (Table 4) [10].

Consultation of an anesthesiologist to provide sedation is suggested in patients with a performance status assessed by ASA classification of ≥III (according to ESGE guidelines), ≥IV (according to both ASA and ASGE) or airway assessment Mallampati's class III or IV [1,5]. Primary involvement of an

Table 3 Classification of physical status according to the American Society of Anesthesiologists (ASA)

Stage	Performance status
I	The patient is normal and healthy
II	The patient has mild systemic disease that does not limit activities
III	The patient has moderate or severe systemic disease that does not limit activities
IV	The patient has severe systemic disease that is a constant threat to life
V	The patient is morbid and is at substantial risk of death within 24 h
E	Emergency status: in addition to the underlying ASA status, any patient undergoing an emergency procedure is indicated by suffix "E"

Table 4 Airway assessment according to Mallampati score

Class	Airway assessment
I	Full visibility of the tonsils, uvula and soft palate
II	Visibility of the hard and soft palate, upper portion of the tonsils
III	The soft and hard palate and base of the uvula are visible
IV	Only the hard palate is visible

Table 5 Schematic summary with the 5 necessary steps for a patient's initial assessment and administration of sedation

Step	Patient assessment and sedation administration
1	Evaluate the patient's ASA status
2	Obtain informed consent
3	Ensure that a pulse oximeter, an O_2 supply source, a suction device and the appropriate airway patency equipment are available
4	Administer benzodiazepines and/or analgesics
5	Administer propofol only in interventional endoscopic procedures and in patients with ASA score I-II

ASA, American Society of Anesthesiologists

anesthesiologist is also required in case of anatomic oropharyngeal variants predicting difficult endotracheal intubation, prolonged endoscopic procedures requiring deep sedation or anticipated intolerance to standard sedatives [6] (Table 5).

Is patients' consent necessary for the administration of sedation during endoscopy?

Statement 2: Informed documented consent for the administration of sedation is necessary and should be obtained by the physician who will perform the endoscopy.

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***100%***

Medicolegal issues are important when considering sedation in endoscopy, for 2 main reasons: i) up to half of the complications after endoscopic procedures are related to sedation; and ii) in several studies, the majority of endoscopists cited "medicolegal issues" as the main reason for not administering sedation [11-13]. Informed consent for sedation during endoscopy should be obtained from the patient or his/her legal representative according to the Greek laws and regulations, in a way similar to that used in the case of other endoscopy procedures [Law 4715/2020]. It is generally obtained during a face-to-face discussion between a physician familiar with the procedure and the patient, with information given to the patient in comprehensible language and the opportunity for him/her to ask questions prior to the procedure. Information pertaining to the sedation that the patient will undergo should include the following: the pros and cons of sedation, with the provision of an alternative option in patients who do not wish to receive sedation (i.e., the option for unsedated endoscopy); potential complications and post-procedure risks related to the procedure, such as driving, operating equipment or any other function where psychomotor functions are essential, consuming alcohol or drugs, and taking legally binding decisions; and the patient should also be informed about the risk of amnesia related to the time of the endoscopy. The informed consent regarding sedation issues may be incorporated into the main body of the endoscopy consent form, while the procedure of informed consent needs to be documented [1].

Section 2. Monitoring of the patient and equipment needed for the administration of sedation

What is the appropriate monitoring of a sedated patient during endoscopy?

Statement 3: Appropriate monitoring of the sedated patient during endoscopy should include clinical evaluation of their level of consciousness and monitoring of cardiorespiratory function and hemodynamic stability.

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***100%***

The appropriate monitoring of the sedated patient during endoscopy requires the presence of sufficiently trained physicians and non-physician ancillary personnel and depends on the degree of sedation (moderate or deep), the type of drugs delivered and the patient's physical status according to the ASA [9].

In particular, when moderate sedation (grade I-II, International Classification of Repression) is used on patients with ASA I-III physical status, monitoring may be performed by a single suitably trained nurse, who can also perform short interruptible tasks (e.g., biopsy) under the supervision of the endoscopist [14-16]. However, in complex

endoscopic procedures (e.g., difficult polypectomy), the presence of a second assistant, responsible for the technical requirements of the endoscopy, is required, allowing the nurse administering sedation to focus on monitoring the patient [6,16]. The administrators of sedation should have the skills to diagnose and manage sedation-related adverse events, including rescue from a level of sedation deeper than that intended [5]. In severely ill patients (ASA IV and V), in patients with a history of side-effects or complications during sedation and anesthesia, when deep sedation (level III-IV) is used, and in high-risk endoscopies, monitoring should be performed by an appropriately trained and accredited medical specialist, or preferably by an anesthesiologist/anesthesiology team, in organized health care units [16]. The presence of an anesthesiologist is also recommended for propofol-sedated patients of ASA class ≥III, patients with a Mallampati's class ≥3 or conditions that put them at risk of airway obstruction (e.g., pharyngolaryngeal tumors), in narcotic analgesic drug users and in prolonged endoscopic procedures [1].

For patients receiving intravenous sedation, vascular access should be maintained throughout the procedure and until the patient is no longer at risk for cardiorespiratory depression [6]. A nasal catheter for supplemental oxygen is required during endoscopy. It is also necessary to set the alarm limits in the patient's vital signs monitoring device and to record all drugs given, as well as the patient's level of consciousness, ventilatory and oxygenation status, hemodynamic variables and any adverse event, before the administration of sedative/analgesic agents, immediately after administration of the medication, at regular intervals during endoscopy, at the end of the endoscopy and initial recovery, and just before discharge [5,17]. Monitoring the patient receiving moderate procedural sedation [6,17,18], includes:

(a) Regular and continuous (at least every 5 min) clinical assessment of the level of consciousness at baseline and until the patient awakens, as assessed by verbal (if possible) response to simple commands or other forms of bidirectional communication. The use of the Bispectral Index/electroencephalogram is not routinely recommended, although it appears to improve the estimated propofol dose and prevent the risk of over-sedation [19,20]. The patient's facial expression is also assessed as a good indicator of the level of discomfort experienced.

(b) Assessment of respiratory function (ventilation function and oxygenation) using a pulse oximeter, as well as visual examination and continuous observation of clinical signs such as amplitude, rate and pattern of respiration. Capnography is not routinely recommended, but it is considered useful in intended deep sedation and in high-risk patients, and in prolonged procedures (endoscopic ultrasound [EUS], endoscopic retrograde cholangiopancreatography [ERCP]) when propofol is administered [1,6].

(c) Control of hemodynamic stability, by continuous monitoring of heart rate and intermittent automated noninvasive blood pressure measurement (at baseline and then at 5-15-min intervals, and every 3-5 min when administering propofol or deep sedation), until the patient has completely recovered. Continuous electrocardiographic recording is recommended in selected patients with significant cardiovascular diseases or dysrhythmia, while it is considered useful in the elderly, and in patients with severe pulmonary diseases, or in prolonged procedures [1,5,6,16].

When does this monitoring end?

Statement 4: The monitoring of the sedated patient ends when the basic level of consciousness has been recovered and the patient is no longer at risk for cardiorespiratory depression.

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***100%***

Although adequate discharge standards following sedated endoscopy have not been established, continuous monitoring of SpO_2 and periodic assessment of the level of consciousness, cardiorespiratory function and motor adequacy at regular intervals are suggested for a sufficient amount of time (at least 1 h), in an appropriately staffed and equipped area, in close proximity to the location where the sedation was administered. This should be until the baseline level of consciousness has been restored, and there is no further risk of cardiorespiratory depression [1,5,6]. The Aldrete score [21], the post-anesthesia discharge scoring system [22] or the modified post-anesthesia discharge scoring system [23] can be used in this context, and all parameters assessed at the time of determination should be written into clinical records. Patients receiving IV sedation on endoscopy should be discharged, preferably accompanied by a responsible adult chaperon, and should refrain from driving, operating heavy machinery or engaging in legally binding decisions for at least 12 h (24 h in cases where combined agents for sedation are used, 6 h in patients ASA 1-2 who have received only propofol) [1,6].

What is the minimum equipment required to administer sedation in the endoscopy room?

Statement 5: The minimum equipment required for the administration of mild-to-moderate sedation includes a pulse oximeter, an O_2 supply source, a suction device and the appropriate airway patency equipment. For deep sedation anesthesiological support is needed.

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***100%***

The minimum equipment required to administer sedation in the endoscopy room is similar for gastroenterologists performing endoscopies in hospitals and in private practice and includes the following:

For mild-to-moderate sedation [14,17]:

- Venipuncture equipment: gloves, elastic cuff, cotton, alcohol, catheters, syringes, intravenous fluids, plasterer
- Stethoscope
- Electronic instruments (monitors) for monitoring saturation (pulse oximeter), pulse blood pressure, with audible alarm of lower limits.
- O_2 supply (oxygen cylinders type E or central supply), nasal oxygen catheters, extension
- Suction device with the corresponding catheters
- Airway patency equipment suitable for the patient's age and sex: masks, esophageal ducts, Ambu device, laryngeal mask, lubricant
- Medicines: medicines used for sedation, their antagonists and emergency medicines (adrenaline, atropine, cortisone, glucose, nitroglycerin) should be stored in a suitable and safe place, easily accessible during endoscopy. The expiration date of the medication should be checked at regular intervals.

For deep sedation [14,24]:

All the above as metioned for the administration of mild to moderate sedation with the addition of anesthesiology support with the appropriate equipment. Section 3. Training of the endoscopists who administer sedation.

Is sedation training required for endoscopists who perform sedation?

Statement 6: Sedation during endoscopy is administered by sufficiently trained physicians and non-physician ancillary personnel, who should undergo constant training.

100% agreement

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***100%***

The need for appropriate training, irrespective of the type of sedation used during gastrointestinal endoscopy, for all clinical staff, physicians and non-physician ancillary personnel, has already been endorsed, as part of quality assurance, by numerous professional gastroenterology societies and teams of experts in Europe [25-27], Japan [6], and the USA [5]. Unfortunately, sedation training is not included in the curriculum of gastroenterology fellows in Greece and no relevant legislation exists.

The necessary theoretical and practical components of this training (e.g., Basic Life Support [BLS], Advanced Cardiovascular Life Support [ACLS], knowledge of pre-sedative assessment, level of sedation appropriate for each endoscopic procedure, sedative drugs and antagonists with their pharmacokinetic and pharmacodynamic properties, patient monitoring, recovery care, assessment and management of sedation-related complications, discharge) as well as how the competency is being assessed, documented, monitored and updated, should be determined separately by a team of experts, according to already published guidelines and curricula [25,27,28].

Section 4. Drugs used for sedation: sedatives and analgesics

Which drug categories are used for induction of sedation/ analgesia in endoscopic procedures?

Statement 7: Apart from local anesthetics, during endoscopic procedures patients receive sedatives (such as benzodiazepines and propofol) and/or analgesics (such as opioids) in titrated doses, to achieve the desired level of consciousness, depending on the type of the procedure, and the patient's age and general medical status.

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***100%***

Drug categories commonly used are [5,18,28,29]: 1) local anesthetics; 2) sedatives; 3) analgesics; and 4) antagonists. Local anesthetics in the form of spay or gel are used for local analgesia and to diminish the oropharyngeal reflex. Sedatives are administered intravenously, either alone or in combination with analgesics (particularly opioids), in titrated doses and over short time intervals in order to achieve the desired level of unconsciousness. This level depends on the type of the endoscopic examination, the expected duration, and the patient's age and general condition as evaluated prior to the procedure (ASA classification) [27]. Finally, the antagonists are used to reverse the action of the main drug(s) and for quicker and safer recovery after the examination, or for improvement of the level of consciousness, if necessary, during the endoscopic procedure [30,31].

Which benzodiazepines should be administered during the endoscopic procedures and what is their way of action?

Statement 8: The benzodiazepines mainly recommended for sedation during endoscopy are primarily midazolam and alternatively diazepam, both administered intravenously.

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***100%***

Benzodiazepines have been used, alone or in combination with an opiate, to achieve mild to moderate sedation in patients undergoing upper or lower gastrointestinal endoscopy, diagnostic or therapeutic [32]. The most commonly used benzodiazepines are midazolam and diazepam, both administered intravenously. Although oral midazolam (7.5 mg, 20 min before endoscopy) has been used, data are limited on the efficacy of this route of administration [33].

Benzodiazepines minimize stress, cause drowsiness and transient amnesia, enhance the action of other co-administered drugs, but have no analgesic effect. They should be administered gradually in doses every 2-5 min to assess the sedation they cause and to avoid overdose and complications, especially in the elderly and in combination with opiates. Their onset of action is 1-3 min and the effects last 10-40 min, while in the elderly, obese and patients with hepatic impairment recovery may be delayed.

The efficacy of the suppression with these 2 benzodiazepines is comparable and there are no differences in the frequency and severity of hypoxemia in equivalent doses (3.4: 1, diazepam: midazolam) [34]. However, midazolam is slightly superior because of its faster onset of action, shorter duration of sedation, lower risk of thrombophlebitis and stronger amnesia [35-38]. An advantage of benzodiazepines is the availability of an antidote (flumazenil) that, given intravenously, directly inhibits the sedative effect of benzodiazepines and must be readily available in any endoscopy unit.

When is the combination of analgesics with sedatives needed during an endoscopic procedure?

Statement 9: The use of analgesics in combination with sedatives, especially for endoscopies anticipated to cause higher levels of pain and discomfort or to have longer duration, may reduce the patient's discomfort and pain, and increase endoscopist comfort.

93% agreement

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***93%***

Sedative drugs lack analgesic properties; therefore, the use of analgesics in combination with sedatives may be required to reduce the patient's discomfort and pain, especially for endoscopies anticipated to cause higher levels of pain and discomfort or to have longer duration.

Non-complex endoscopies, such as gastroscopies and colonoscopies, can be performed under conscious sedation using only sedatives, although the combined use of sedatives plus analgesics might be a better option. In studies that compared midazolam as a single agent with midazolam plus analgesics (fentanyl or meperidine), the combination showed improved tolerance of the procedure, decreased levels of pain and higher operator satisfaction [39-41].

For complex and prolonged endoscopic procedures such as ERCP, adequate pain control is an important aspect to consider. It has been reported that between a third and a half of patients undergoing ERCP under conscious sedation experience discomfort and pain, implying that pain was often under-treated during and after these procedures [42]. The use of opioids in combination with midazolam or propofol resulted in higher analgesic effects and better patients' and endoscopists' comfort [43-45]. There are no controlled trials comparing sedatives and sedatives plus analgesics that focus on examination/treatment other than ERCP [42,43].

Coadministration of analgesics and opioids increases the depth of sedation; therefore, careful dose adjustment and titration is mandatory given their synergistic effect on the risk of cardiorespiratory depression [46].

Compared with meperidine, fentanyl has a faster onset of action and a shorter half-life; thus, it has been associated with a shorter recovery time and total procedure time for both esophagogastroduodenoscopy and colonoscopy [47,48].

For elderly patients or those with higher ASA scores, a ≥50% dose reduction is indicated. For these patients the initial dose should be lower and titration should be more gradual to allow assessment of the full effect at each dose level.

Young children and infants are more sensitive to sedative and opioid drugs than adolescent and adult patients and also have psychological and anatomical considerations that require specific training. NICE guidance exists for practitioners intending to administer sedation to children and young people [49]. In general, in advanced endoscopic procedures, deep sedation or general anesthesia might be preferred over conscious sedation.

Section 5: The use of propofol

What is the role of propofol in sedation during endoscopy?

Statement 10: The use of propofol is superior to the classical sedation drugs during interventional endoscopic procedures because the patient's satisfaction is greater and the recovery time is shorter.

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***100%***

Studies have shown that propofol is superior to traditional sedation schemes of benzodiazepines plus opioids in ERCP procedures. Higher post-procedure patient satisfaction is achieved with propofol compared to traditional sedation for colonoscopy, endoscopic ultrasonography, ERCP, but not gastroduodenoscopy [5,8,19,27,50,51]. Time to sedation and recovery time are shorter with propofol than with traditional sedation. Regarding adverse effects, propofol may relatively frequently cause hypoventilation, hypotension and bradycardia, but severe adverse effects are extremely rare [52,53].

Synergistic sedation with low doses of intravenous midazolam and propofol significantly reduces the required dose of propofol and therefore the risk of complications; it has been reported to be an effective alternative option to the use of propofol as a sole agent [54,55]. Propofol as a sole agent and synergistic sedation with low doses of intravenous midazolam and propofol have also been proposed for gastrointestinal endoscopy in children [55].

Despite the adequate safety data from non-anesthesiologists administering propofol, the majority of the anesthesiology community remains opposed, because of the drug's ability to quickly induce deep sedation and general anesthesia [56]. Since there is no reversal agent for propofol, the likelihood that advanced airway management techniques will be needed is higher than for the combination of midazolam with opioids. Moreover, sedation is a continuum, and deep sedation is logically associated with an increased frequency of inadequate ventilation or airway obstruction. Thus, the anesthesiology community recommends that propofol-based sedation should be administered only by anesthetists.

Simple endoscopic procedures can be performed with moderate sedation, maintaining a high degree of patient

satisfaction. Propofol-based sedation is not recommended for cases assigned to moderate sedation, because of patient intolerance at this sedation level. Prolonged or complex procedures are frequently performed under deep sedation, when the use of propofol-based sedation is strongly recommended.

The ESGE [1] and ASGE [6] recommend the use of propofol-based sedation directed by endoscopists and registered nurses in selected patients with low and medium risk when it is expected to improve patient safety and comfort, procedural efficiency and/or successful procedure completion. Endoscopists and nursing stuff should be board certified in intensive medicine and resuscitation to ensure the patient's comfort and safety. The providers should be properly trained in the administration of endoscopic sedation and should possess the skills necessary for the diagnosis and management of sedation-related adverse events, including rescue from a level of sedation deeper than that intended [57,58]. Greek studies have shown that propofol-based sedation has not largely been adopted by the endoscopic community, mainly because of medicolegal reasons and inadequate training [31,59].

Section 6. The presence of an anesthesiologist

Can non-anesthesiologists administer propofol during endoscopy?

In which cases should an anesthesiologist be present?

Statement 11: Propofol can be administered by gastroenterologists, in endoscopy rooms adequately equipped and in patients with ASA score I-II.

Rounds of voting needed to reach agreement: ***2****; Agreement level:* ***94%***

Statement 12: If the above requirements are not met, and/or in patients with ASA score >III an anesthesiologist should be present

Rounds of voting needed to reach agreement: ***2****; Agreement level:* ***94%***

Although the anesthesiology community recommends that propofol-based sedation should be administered only by anesthetists [60,61], there is a growing body of evidence to support the administration of propofol by non-anesthesiologists, sufficiently large to be included in the guidelines of large scientific societies (ESGE, ASGE, Japanese Society of Gastroenterology, and others) [1,5,6].

Endoscopists may administer propofol after completing both theoretical (pharmacology, pharmacokinetics, patient monitoring, patient selection) and hands-on (basic and advanced airway management, management of respiratory distress, Basic Life Support and Advanced Cardiovascular Life Support) training [62,63]. It is recommended that a single member of the team is solely responsible for the administration of propofol and patient monitoring [52]. The following provisions are to be taken: secure IV access [64], administration of supplemental oxygen [65], continuous pulse oximetry, and blood pressure monitoring.

This practice can be safely performed in adequately-equipped endoscopy rooms (suites with equipment to secure the airway, ventilate the patient and correct hypotension) for diagnostic gastroscopies and colonoscopies in patients with ASA scores <3. In patients with ASA scores ≥3, difficult airway management, chronic use of analgesia medication or longer procedures, sedation should be administered by an anesthesiologist [66].

Patients undergoing longer and/or therapeutic procedures, such as ERCP, EUS, assisted enteroscopy or emergency hemostasis, or those with a history of substance of ethanol abuse, require a deeper sedation level and are thus better managed by an anesthesiologist [28].

It is worth mentioning that the Greek legislation states that "properly trained physicians" are allowed to administer propofol, without specifying their medical specialty [https://pharmalist.gr/spc/SPC_3241401_1.pdf]. Sedation training is broadly included in the curriculum of gastroenterology fellows [FEK 1401B'/23.04.2019;pages 16722,16725].

Are sedated endoscopy examinations safe for patients with special conditions or chronic diseases (heart disease, chronic obstructive pulmonary disease [COPD], chronic renal failure [CRF], myasthenia gravis, pregnancy, seniors, psychotropic drug administration, hepatic cirrhosis)?

Statement 13: Sedated endoscopy examinations can be safely conducted on patients with special conditions or chronic diseases, provided that the endoscopist evaluates both the patient's ASA status and the complexity of the endoscopic procedure in order to provide mild-to-moderate sedation.

Rounds of voting needed to reach agreement: ***2****; Agreement level:* ***93%***

Based on the ASA physical status classification, patients with severe, chronic, systemic, serious life-threatening diseases have been classified as class IV (of 6 classes) [9]. Therefore, patients with heart diseases (e.g., ischemic disease that could cause anginal attacks or heart failure, etc.), COPD, CRF, myasthenia gravis, hepatic cirrhosis, seniors (>70 years), with age-related functional diseases of the heart, lungs, kidneys, liver, endocrine system and nervous system, should undergo a consultation with an anesthesiologist or the respective specialist prior to the endoscopy, to decide on the appropriate sedation, considering the underlying disease. Suitable monitoring should be applied during and after the endoscopic procedure [1,5,6,67]. Moreover, the 2018 revision of the ASA guidelines [17] recommends for all patients the following strategies: i) review medical records for underlying medical problems (e.g., abnormalities of major organ systems, obesity, obstructive sleep apnea syndrome, anatomical airway problems, congenital syndromes with associated medical/surgical issues, respiratory disease, allergies, surgery history, psychotropic drug use, current medications or use of non-pharmaceutical substances etc.); ii) physical

examination; and iii) pre-procedure laboratory testing (where indicated). Pregnancy is a special clinical condition that similarly needs elective administration of sedatives and monitoring by an anesthesiologist before, during and after endoscopy, in view of the potentially difficult airway ventilation and possible effects of the sedative on the fetus (e.g., hypoxemia, hypotension or teratogenesis) [5,6]. Based on the above, in the presence of patient-related risk factors for complications, the primary involvement of an anesthesiologist during endoscopy is suggested [1]. Furthermore, according to the ASA, if a practitioner confronted with the likelihood of sedation-related adverse events—e.g., ASA class IV (the patient has a severe systemic disease that is a constant threat to life, such as severe congestive heart failure or end-stage renal failure)—is not trained in the rescue of patients under general anesthesia, an anesthesia professional should be consulted [24]. Finally, for patients with special problems or chronic diseases who are ASA class II (mild systemic disease not limiting activities, such as controlled hypertension or controlled diabetes without systemic sequelae) or possibly ASA class III (moderate or severe systemic disease not limiting activities, such as stable angina or diabetes with systemic sequelae), minimal and/or moderate sedation can be delivered safely by endoscopists [5].

Based on the above, every gastroenterologist/endoscopist should know the ASA classification and evaluate it in each patient who is going to undergo an endoscopic procedure.

Which is the most appropriate method for sedation during urgent endoscopy?

Statement 14: During urgent endoscopy in severely ill patients whose cardiorespiratory function is compromised, assistance from an anesthesiologist is recommended. In the remaining cases, the recommended sedation is via titrated administration of a sedative with a relatively short half-life and an action that is or is not reversible.

Rounds of voting needed to reach agreement: ***2****; Agreement level:* ***88%***

Based on the available literature, urgent (≤12 h) endoscopy in the gastrointestinal tract is considered a high-risk procedure [1,5,6,18,68].

Hemodynamic alterations, as well as evident or eminent respiratory distress due to impaction and/or vomiting in patients with underlying cardiac or respiratory diseases, tend to increase the risk for sedation-related adverse events [24,67-70]. For that reason, available guidelines encourage the involvement of anesthesiologists and anesthesia provider-administered sedation during urgent endoscopy in patients who have active, ongoing bleeding and/or are at high risk for endotracheal intubation, as well as those with an ASA classification >III [5,6,11,18,68]. This practice is also fully compliant and compatible with Greek legislation [Law 4715/2020/FEK 149/A/1-8-2020].

Unless urgent endoscopy is being performed in high-risk patients, sedation can be provided under constant cardiorespiratory monitoring from qualified non-anesthesia providers [71,72]. Low-quality evidence, along with its widespread use among gastroenterologists in Greece, encourages the use of carefully titrated short-acting benzodiazepines whose sedative effect can be reversed through the administration of an antagonist [6,31,4,73]. Midazolam is commonly used for this purpose, as it does not cause hypotension or hypoxia in regular doses, exhibits a rather short half-life and has a sedative effect that can be reversed by flumazenil [6,31,4,73]. During the past few years, there has been increasing interest in a new generation benzodiazepine, remimazolam, due to the rapid onset and "deterioration" of its sedative effect along with a more favorable safety profile: remimazolam is not associated with cardiovascular or respiratory suppression, even in older patients or those with ASA >III [74,30].

Based on results from non-randomized trials, propofol can be utilized as a sedative for stable ASA I-III patients undergoing urgent endoscopy, provided that the personnel present in the endoscopy room are familiar with its use, dosing regimens and side-effects, and are capable of providing effective life support, if required [6,11,72,75]. Propofol use may prove helpful if a cumbersome, demanding procedure is anticipated, which will also require optimal patient "compliance" [6,18,26,72,75].

During urgent endoscopy in patients who have high theoretical risk for aspiration because of hematemesis, vomiting or food bolus/foreign body impaction, the potential of opioids to suppress the cough reflex, induce emesis and cause functional esophagogastric junction outlet obstruction or spastic esophageal activity should be taken into consideration [76,77].

Regarding the use of dexmedetomidine or ketamine for sedation during urgent endoscopy, although the data appear encouraging, no safe conclusions can be drawn as there is a lack of sufficient evidence [30,78]. The lack of experience and familiarity of gastroenterologists nationwide with the use of both sedatives further discourages their use at this point.

Section 7. Sedation antagonists in endoscopy

Is the use of sedation antagonists recommended for the reversal of sedation administered during endoscopy?

Statement 15: The administration of sedation antagonists for the reversal of sedation is recommended for patients with respiratory suppression unresponsive to verbal commands.

Rounds of voting needed to reach agreement: ***1****; Agreement level:* ***100%***

Moderate sedation includes the use of a fast-acting benzodiazepine, such as midazolam, in combination with an opioid analgesic to reduce both anxiety and pain. The combination allows the use of lower doses of both drugs. It is important to administer drugs in small increments to avoid oversedation. Elderly persons should be given lower doses to avoid respiratory suppression [28].

Despite careful and gradual sedation, oversedation can occur and it may sometimes be accompanied by respiratory arrest or suppression, putting the patient's life at risk. Immediate measures should be taken for respiratory and life support, along with the use of sedation antagonists to reverse the action of the sedative and analgesic medications in case of non-improvement. If the procedure has been successfully completed, full reversal of the sedation should be performed. If the procedure has to be continued, partial reversal of sedation can be tried, so that the endoscopist may be able to continue with light sedation and verbal communication with the patient, who should respond with eye movements and gestures [79].

Flumazenil is an effective fast-acting benzodiazepine antagonist that can immediately reverse benzodiazepine's action and respiratory suppression. Its short duration of action may require monitoring of the patient and repeated increments to avoid recurrence of respiratory delay. In one study, the administration of flumazenil 10 min after completion of upper endoscopy led to a shortening of recovery time, without influencing other factors such as treatment memory, satisfaction and overall discomfort. In another study in patients who underwent upper endoscopy under midazolam sedation, flumazenil was superior to placebo (given immediately after the end of the procedure) for patient recovery and cooperation 5 min after the end of the procedure, while there was no difference in memory or in psychomotor and regulatory functions after 3.5 h. Flumazenil has rarely been reported to cause convulsions or anxiety attacks, especially in chronic benzodiazepine users or patients with a relevant history [80,81].

Naloxone hydrochloride is a potent opioid receptor antagonist metabolized in the liver into naloxone-3-glucoronide. It can reverse respiratory suppression, sedation, analgesic effect, papilla muscle contraction and delayed gastric emptying caused by opioid overdose. However, it has significant side-effects, such as hypertension, tachycardia, ventricular fibrillation, pulmonary edema, vomiting and convulsions, and can cause acute withdrawal syndrome in chronic opioid users. Because of its suboptimal safety profile, naloxone should be reserved for severe cases or respiratory suppression when life support and flumazenil are not effective [82].

Which data should the endoscopist record in the endoscopic report?

Statement 16: The medication administered, including dosage, the vital signs and events (if any) during and after the procedure, and the patient's full recovery before discharge from the endoscopic unit should be reported.

Rounds of voting needed to reach agreement: ***2****; Agreement level:* ***86%***

The data required to be included and recorded by the endoscopist in the report provided to the patient after endoscopy should include the following: (i) the vital signs assessed during endoscopy, as well as 1 h after completion of the procedure; (ii) the drugs administered during endoscopy and the dose at which they were administered; (iii) whether the patient was alert and time-oriented at the time of departure from the endoscopic unit; iv) the recommendation for the patient to be at home, especially during the night, with an attendant, who should be a responsible adult, to report any complications as a consequence of the procedure; and (v) the telephone number of the clinic or the doctor, to be called in case of an emergency [83]. The entry of all the above data into an electronic database can contribute to better monitoring and documentation of quality during endoscopy and can also be used as an appropriate file in the case of medical or legal research [84].

Final comment

The main problem in Greece at present is the lack of relevant legislation regarding the administration of sedation by non-anesthesiologists. To solve this problem, the Hellenic Society of Gastroenterology is planning to submit our position statement to the Greek Ministry of Health, along with our thesis regarding this matter, and to organize BLS and ACLS training by a team of experts, including anesthesiologists, according to published curricula. Courses must be accredited by the Greek State and organized into initial and follow-up courses, with training logs to maintain accreditation.

Concluding remarks

This manuscript consists of 16 position statements prepared and voted upon by panelists on behalf of the Hellenic Society of Gastroenterology, regarding the use and administration of sedation during gastrointestinal endoscopy. The position statements provide guidance on the administration of sedation by non-anesthesiologists, identifying the most common drugs with their modes of action, safety profiles and limitations. These data are expected to aid Greek gastroenterologists in their effort to optimize the management of patients undergoing endoscopic procedures.

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