

Special Article - Digestive Endoscopy

Sedation and Monitoring for Gastrointestinal Endoscopy: Worldwide Attitudes and Evidence

Fanti Lorella¹, Gemma Marco², Rossi Gemma^{1*}, Agostoni Massimo² and Testoni Pier Alberto¹

¹Division of Gastroenterology and Gastrointestinal Endoscopy, Vita-Salute San Raffaele University, Italy

²Department of Anesthesiology, Vita-Salute San Raffaele University, Italy

*Corresponding author: Gemma Rossi, Division of Gastroenterology and Gastrointestinal Endoscopy, Vita-Salute San Raffaele University - Scientific Institute San Raffaele, via Olgettina 60 20132 Milan Italy, Tel: 39 02 26436303; Fax: 39 02 26433491; Email: rossi.gemma@hsr.it

Received: November 28, 2014; Accepted: January 27, 2015; Published: January 29, 2015

Abstract

Sedation and analgesia during gastrointestinal endoscopy is still a matter of debate. The optimal sedation strategy should be pre planned before endoscopic procedure and tailored to the patient, based on specific risks and type of procedure.

Use of sedation during GI endoscopy has increased worldwide over the last 15 years although it varies from a country to another: some surveys around the world have investigated this issue.

Most procedures are performed under moderate sedation combining benzodiazepine with opioid but endoscopic procedures have increased in number and complexity and some drawbacks have emerged.

The introduction of propofol has changed gastroenterologists' and patients' attitude toward sedation and several studies have indicated that propofol is more effective and safer than standard sedation for reaching and maintaining an adequate sedation level during endoscopy, since it provides easier titration of the desired sedation level and a shorter recovery time. Nevertheless its narrow therapeutic window and the lack of reversal agents actually increases the risk for complications in cases of inappropriate administration, so that its use by non-anesthesiologists requires prominent clinical experience and has been limited in many countries. However many studies have shown that non-anesthesiologist propofol sedation is safe and effective if appropriate patient selection is applied and non-anesthesiologist sedation providers have acquired adequate skill and knowledge through dedicated theoretical and practical training programs.

In conclusion, sedation practices differ from one country to another country reflecting many different factors including costs, availability of drugs, devices and professional training courses on cardiopulmonary resuscitation.

Keywords: Sedation; Monitoring; Gastrointestinal Endoscopy; Survey; Propofol

Introduction

As Gastrointestinal (GI) endoscopy is performed, delivering adequate sedation and analgesia is now considered integral part of the endoscopic procedure and a quality index of it.

It is definitely accepted that a specific sedation/analgesia strategy should be decided before the beginning of endoscopy taking into account both patient's characteristics and procedure's requirements. Nevertheless some unresolved questions still remain about this issue. Moreover patients' attitudes and expectations are rapidly evolving when facing the sedation/analgesia issue.

Analgesia is defined as either centrally or peripherally mediated reduction or suppression of pain. Sedation is defined as a drug-induced depression in the level of consciousness, which ranges in a continuum from minimal anxiolysis to general anesthesia. Most endoscopic procedures are performed under moderate sedation combining benzodiazepine and opioids. Therapeutic endoscopy is particularly challenging, since it is unpleasant, time consuming, and still requiring complete cooperation from the patients.

As endoscopic procedures grew in number and complexity, several difficulties emerged. Deeper levels of sedation are needed with increasing frequency and are usually provided by bolus intravenous benzodiazepines with opioids, but during prolonged operative procedures it may be difficult to obtain optimal titration of these drugs. Delayed onset of sedation and significant post sedation side effects, including nausea, vomiting and prolonged recovery time, are at stake.

In this setting the introduction of propofol into clinical practice notably changed gastroenterologists' and patients' attitude towards sedation. Its easy titrability and apparent paucity of side effects made propofol a drug of choice, increasingly used to provide deep sedation during GI endoscopy.

Nevertheless a wide spectrum of sedation strategies for GI endoscopy in adult patients is reported worldwide, with a variability related to difference in health care systems, regulations, and availability of drugs. This is somewhat expected, since sedation impact several aspects of the endoscopic procedures enhancing patient cooperation, endoscopist satisfaction and technical quality of

the examination, but it increases costs and the risk of complications. Whereas the United Kingdom, Scandinavia, Spain, Italy, and Greece benefit from tax-based national health systems, central and eastern European countries depend on more or less privately funded social health systems [1].

The high individual variability in perceiving pain and discomfort during endoscopy adds to the variability in operators' attitude towards sedation/analgesia in this setting. Chatman N et al. reported that, when asked about their expectations about sedation and analgesia during colonoscopy, most of the patients expected to be in a state of complete unconsciousness and many patients interpreted any awareness during previous colonoscopy as a problem related to inadequate sedo-analgesia [2].

Surveys

In spite of its aforementioned geographical variability, sedation/analgesia implementation during GI endoscopy increased worldwide over the last 15 years. In 2005 the results of a nationwide survey have been published in Switzerland: conscious sedation was used in 77% of diagnostic upper endoscopies and 78% of colonoscopies [3]. These frequencies were lower than those reported in a former USA nationwide survey [4], which reported sedation as a standard practice throughout the country, being implemented in up to 98.2% of upper diagnostic endoscopy (EGDS) and 98.8% of colonoscopy. The Switzerland survey reported that procedures were routinely monitored by 73% of the respondents during EGDS and 79% during colonoscopy. In the USA survey vital signs were routinely monitored in more than 98% of cases. By that time only sparse data were available about sedation practice in other European country and throughout the world.

A 2006 European Society of Gastrointestinal Endoscopy (ESGE) survey amongst its members [5] showed that less than 25% of patients undergoing routine diagnostic upper endoscopy received any sedation. Moreover in 62% of the endoscopy units patients were not asked their preferences about sedation and did not sign any informed consent form addressing the sedation regimen.

In 2008 Benson et al. reported the results of an internet-based survey amongst endoscopy unit leaders affiliated to the World Organization of Digestive Endoscopy, with the aim of collect data about sedation practices in developing and developed countries [6]. One-hundred-sixty-five endoscopist with leadership in the international endoscopy community responded, covering a sample of 81 extra-USA countries. They indicated that a benzodiazepine/opioid combination was the most employed sedation scheme and it was applied in around 40% of upper and 56% of lower endoscopies, with comparable features between developed and developing countries. Only few respondents reported that endoscopy without sedation was the prevalent practice in their centres, again without significant differences between developing and developed countries. An increase in the use of propofol with a parallel reduction in benzodiazepine/opioid use was reported by 79% of respondent. Most respondents (more than 87%) routinely monitored vital signs and O₂ saturation, both in developed and developing countries. This cornerstone study had two major limitations: respondents' answers could reflect personal positions about sedation practice rather than the standard practice in their country, and the response rate was poor (51%).

In 2009 two surveys addressed endoscopic sedation and monitoring during GI endoscopy in Spain [7] and in Greece [8] respectively.

In comparison to the USA and the Swiss surveys, the Spanish study showed that the use of sedation during GI endoscopy was relatively uncommon, although greatly variable: sedation rate was low during upper endoscopy (only 27% of Spanish GI Endoscopy units used sedation in more than 50% of their procedures), but higher for colonoscopy (57% of units sedated more than 50% of patients submitted to colonoscopy). In advanced endoscopic procedures, such as cholangiopancreatography (ERCP), sedation was routinely administered. Pulse oximetry was routinely monitored in 77% of Spanish endoscopy units but vital signs only in 42%.

The response rate of the Spanish survey was higher (65%) than that of the Greek one (40%).

The Greek survey respondents administered intravenous sedation in 64% of upper endoscopy, 78% of colonoscopy and 100% of advanced endoscopic procedures, such as ERCP or Endoscopic Ultrasound (EUS). The vast majority of Greek respondents monitored vital sign and pulse oximetry during endoscopy.

In 2011 a nationwide web survey in Italy was endorsed by the Italian Society of Gastrointestinal Endoscopy in order to evaluate sedation and monitoring practises amongst Italian gastroenterologists [9]. The response rate was 41.4%, similar to that in the Greek survey, lower than in the Swiss study and higher than in the USA one. A major result of this work was that, after publication of the Italian Guidelines for Sedation in Gastrointestinal Endoscopy in 2000 [10] and their update in 2006 [11], sedation for GI endoscopy became standard practice in Italy. Respondents stated that they did not administer any sedation in only 2.2% of upper endoscopies and in only 1.4% of colonoscopies. Sedation was universally administered during any advanced endoscopic technique (ERCP, EUS, and enteroscopy). The large majority of Italian patients submitted to both diagnostic and operative procedures under light to moderate sedation had their vital sign and pulse oximetry monitored.

A more recent study by Nwokediuko et al. [12] evaluated sedation practices for routine diagnostic upper gastrointestinal endoscopy in Nigeria. In this series 48.6% of Gastroenterologists used sedation in 25% of their procedures and 40% use sedation in more than 75% of their procedures. The majority of respondents (77%) did not offer their patients the choice between upper endoscopy with sedation or without it and 71.4% stated that they administered sedation only to uncooperative patients and always after the beginning of endoscopy. Pulse oximetry was implemented by only 57.1% of respondents and 85.7% and vital signs monitoring by 85.7% of them. The Authors concluded that, possibly due to complete absence of national guidelines, sedation practice in Nigeria seemed to be below the standard level recommended by international guidelines.

In China GI endoscopy has been traditionally performed with no sedation and this attitude is still predominant among Chinese patients, as stated by Wang HL et al. in a recent paper [13]. According to this study, the majority of patients chose "unsedated" endoscopy, since its cost was more than three times lower than that for "sedated" endoscopy. Since sedated patients perceived a higher income and

had better medical insurance coverage, the Authors speculated that the ongoing improvement in people's living standard could lead to a spread of sedation during GI endoscopy in China. Anyway the Chinese endoscopists' attitude toward sedation seemed to be influenced by the low sedation rate: only 52.7% of respondents stated that the "sedated" procedure was safe and all of them suggested that the "unsedated" procedure was safe. Such concerns about sedation account for the fact that during sedation vital signs were reportedly monitored in all of the cases.

Propofol

Propofol is an ultra-short-acting intravenous hypnotic drug that gained much popularity because of its rapid onset and recovery time, good amnesic effect, and favourable safety profile. The introduction of propofol into clinical practice positively changed gastroenterologists' and patients' attitude toward sedation. As stated by Triantafyllidis et al. in their recent review [14], propofol could become in the future the preferred sedation agent in gastroenterology.

Several studies indicated propofol's significant advantages over benzodiazepine and opioid for sedation during endoscopy. Two large prospective studies showed that it was more effective and safer than standard sedation for reaching and maintaining an adequate level of sedation during endoscopy, since it provided easier titration of the desired sedation level and a shorter recovery time [15,16]. 2012 Cochrane review [17] evaluating sedative techniques for ERCP showed that patients undergoing ERCP procedures under propofol sedation recover faster and better than those receiving standard sedation with benzodiazepine and meperidine. Data from a 2005 meta-analysis [18] documented how propofol sedation was not associated with an increased risk of complications and during colonoscopy it was even associated with lower complication rates than standard sedation.

These data suggest that propofol should be the preferred choice for endoscopic procedures. Nevertheless its narrow therapeutic window and the lack of any reversal agent actually increase the risk for complications in cases of inappropriate administration, so that its use by non-anaesthesiologists has been limited in many countries and particularly in North America. As a matter of fact, titrating propofol to achieve conscious sedation without inducing general anesthesia requires prominent clinical experience. Moreover personnel in the endoscopic room should be able to promptly and effectively handle severe respiratory depression [14].

Non-anesthesiologist propofol sedation

A worldwide experience on Non-Anesthesiologist Propofol Sedation (NAPS) has been reported in a safety review of more than 640,000 endoscopist-directed propofol sedations [19]. This work suggests that NAPS is safe and effective if appropriate patient selection is applied and the non-anesthesiologist sedation providers have acquired adequate skill and knowledge through dedicated theoretical and practical training programs.

In 2009 the German Society for Digestive and Metabolic Disease published its Guidelines for Sedation for Gastrointestinal Endoscopy [20]. In these guidelines it is stated: "For simple endoscopic examination and in low-risk patients, sedation with propofol should be induced by a properly qualified physician and can then be monitored by an experienced person with appropriate training. This

person must not have any other tasks while monitoring the sedation. Propofol may be administered by a properly trained and experienced person who has this as his or her sole task (recommendation grade A, strong consensus)". Moreover these guidelines pinpointed that anesthesiologist-administered sedation should be considered cost-effective only for patients with a high risk state such as American Society of Anesthesiologists (ASA) risk class grade III or IV [21,22], or pathological and anatomical features associated with a higher risk of airway obstruction during the intervention.

The American Association for the Study of Liver Disease (AASLD), the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA), and the American Society for Gastrointestinal Endoscopy (ASGE) established a pro-NAPS front, in strong disagreement with the American Society of Anaesthesiology (ASA). The governing boards of these four Societies released a position statement about NAPS for GI endoscopy. Their joint statement endorsed an evidence-based assessment on the safety, efficacy and cost-effectiveness of NAPS for GI endoscopy. The Sedation Task Force in charge for this duty was chaired by Cohen LB and included representatives from each of the four societies. Its final document, approved by the governing boards of the four societies, concluded that NAPS was comparable to standard sedation with benzodiazepines and opioids with respect to sedation efficacy and safety profile. The document was published jointly in 2009 in *Gastrointestinal Endoscopy* [23], *American Journal of Gastroenterology* [24], *Gastroenterology* [25] and *Hepatology* [26].

The resulting guidelines stated that, even for operative procedures, NAPS is more cost-effective than standard sedation and that anesthesiologist-administered sedation for healthy, low-risk patients undergoing routine GI endoscopy results in higher costs with no proven benefit with respect to patient safety or procedural efficacy.

In the December 2010 issue of the *European Journal of Anaesthesiology* an evidence- and consensus-based set of guidelines on NAPS for GI endoscopy was published [27]. This document was the result of a collaborative effort from the governing boards of the ASGE, the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) together with the European Society of Anaesthesiology (ESA). These three societies together endorsed the guidelines that were concurrently published in *Endoscopy* [28].

This document fuelled a bitter debate in Europe and, due to the strong opposition from 21 European National Anesthesia Societies [29], the ESA retracted its endorsement [30]. On behalf of the NAPS task force, J.M. Dumonceau strongly took position against this retraction, and stated that, in absence of any new scientific evidence against the published guidelines, the European Gastroenterological Societies continued to endorse them [31]. In a recent editorial [32] the same Author surmised that, despite scientific evidence supporting the use of NAPS, the major obstacles to its expansion are the enormous financial incentives derived from anesthesiologist-assisted endoscopic procedures and the institutional control maintained by anaesthesiologists over sedation policies.

Commenting on the opposition document of the 21 Anesthesia Societies [33] C. Werner stated: The denial of the petition of the American College of Gastroenterology by the US Food and Drug Administration (FDA) cannot be regarded as prohibiting propofol

use by non-anesthesiologist. Instead, it refers to the need for implementation of quality structures and standard within the setting of propofol sedation, which was precisely the aim of the European Society of Anaesthesiology endorsement. The framework provided by the guideline is clearly intended to improve the quality of patient care in countries where non-anesthesiologist administers sedation and analgesia". This topic inspired the joint publication of a multi-society sedation curriculum for GI endoscopy in Gastroenterology, American Journal of Gastroenterology, Gastrointestinal Endoscopy, and Hepatology and on the Society of Gastroenterology Nurses and Associates website [34-38].

In Europe a sedation curriculum has been subsequently published, based on the consensus of gastroenterologists, anaesthesiologists and nurses who have previous been involved in the development of NAPS guidelines for GI endoscopy. The multi-society European curriculum for sedation training was jointly approved and published as position statement by the ESGE and ESGENA [39].

The ensuing divergence among European Anesthesiologists has been stigmatized by Werner C. at al. in a invited commentary in the European Journal of Anaesthesiology: "Whereas one group opposes the guideline through perceived lack of scientific validity and apparent abandonment of anaesthesiologists interest, the other views the approach as an enhancement of safety standards, particularly for those countries currently providing care below the required level. The diverse position among ESA members reflect the different medical practice, reimbursement policies and political leaning within individual countries", and even more: "anesthesiologists in every European nation have a unique opportunity to show leadership in shaping the practice of procedural sedation practitioners. Using our influence and expertise to create the right conditions for skilled sedation can only enhance the quality and safety of sedation practice throughout Europe. It would be unfortunate if fundamentalism and populism were to weaken our position as a profession" [33].

Legal Issues

A consequence of the hurdles that the situation described above poses on NAPS's track is the manufactures' black box warning about propofol administration, stating that only people trained in general anaesthesia can administered it. This manufactures' recommendation reflects propofol's original FDA approval and was developed before the more recent evidence of NAPS's safety and effectiveness. Although for other drugs it has been recognized that labelling may be outdated and does not represent current medical evidence and practice [40], so that off-label use is somewhat justified, the presence of an Anesthesiologist is required by law during propofol administration in most countries. This poses legal threats to Gastroenterologists practicing NAPS. In fact Aisenberg in a 2007 editorial [41] warned that: "to enhance patient safety and practitioner legal protection, leaders in gastroenterology and anaesthesiology must work cooperatively to develop training, certification and quality assurance programs, as well as authoritative practice guidelines for GD-P".

In the Italian survey [9] the majority of respondents declared that after appropriate training they would administer propofol without the presence of the Anesthesiologist. The importance of legal issues in medicine is well known and the respondents who declared they would not use propofol even if properly trained (23.1% of the total

mainly feared cardiopulmonary complications and legal issues. This is similar to what was reported by the Greek [8] and the USA studies [4].

In the absence of case law relating directly to the use of propofol, a definitive view upon the risk of litigation arising from its use under the direction of Gastroenterologist and/or registered Nurses is not possible [42].

Unsedated endoscopy

Sedation for routine endoscopic procedures is widely used throughout the world there are substantial differences in the sedation practice during colonoscopy between countries. In the USA, UK, and parts of Europe, the tendency is to use sedation for almost all colonoscopies while in some European countries such as Germany and Finland, most examination are conducted without sedation [43,44]. Although adequate patient sedation is mandatory during complex and time-consuming interventional endoscopic procedures, there is general consensus that patients should be more involved in the decision whether to receive sedation or not. In discussing this opportunity with patients, several issues have to be taken into account.

Unsedated upper gastrointestinal endoscopy is well tolerated and, as stated by Ladas SD et al [5], in about 50% of ESGE-related countries, less than 25% of patients are sedated for routine diagnostic upper endoscopy.

Local anesthetics are frequently used to anesthetize oral cavity and pharynx to reduce the gag reflex [45,46]. Several studies have shown that anesthesia of the pharynx with lidocaine is useful and effective to make tolerable upper endoscopy without sedation [47,48].

On the other hand unsedated transnasal upper endoscopy has been suggested as a more comfortable and safer method than unsedated transoral upper endoscopy and some study aimed to assess the tolerability, safety, and efficacy of it [49]. However, the numbers of comparative trials are limited.

Sedation less colonoscopy reduces drug-related complications and facilitates patient's position changes during the procedure, and several mechanisms related to the level of sedation could impact polyp detection during colonoscopy [50]. There has been evidence [51] that sedation/analgesia during screening colonoscopy was significantly associated with the likelihood of detecting at least one polyp. Although it could be argued that sedation offers no real advantage on the technical quality of colon examination, since Endoscopists can usually perform a careful examination during colonoscope withdrawal regardless of the level of sedation, Bannert C. et al. [52] reported lower cecal intubation rates due to the pain experienced by patients, with increased risk of missing proximal colon cancers. In this series sedated patients under had more polyps detected in the recto sigmoid area and the Authors suggested that this might be accounted for the longer time to aspirate air and closer mucosal inspection. Polyps are most frequently detected in recto sigmoid area both in sedated and unsedated patients, although polipectomy rates are higher in sedated patients. Polyps in this area might be frequently rated as "harmless" and Endoscopists possibly would to extend their exploration in this pain-generating area. Cecum is more easily reached when sedation is ongoing and the main factor for failed cecal

Table 1: Worldwide practice of sedation-risk-free colonoscopy [53].

(Modified from: Leung FW, Aljebreen AM, Brocchi E, Chang EB, Liao WC, Mizukami T, et al. Sedation-risk-free colonoscopy for minimizing the burden of colorectal cancer screening. *World J Gastrointest Endosc.* 2010; 2: 81-89.

Endoscopist location (N)	Cecal intubation (%)	Special technique	Incomplete/difficult intubation	Predictor(s) of pain	Author
GI (Taiwan) (176)	97.70	As needed sedation colonoscopy (9.6%) or sigmoidoscopy (10.1%)	Intolerance (n=2), technical difficulty (n=1), poor preparation (n=1)	Female gender and the endoscopist	Liao WC et al. [54]
Surgeon (Taiwan) (109)	85.30	Sedation-free colonoscopy	Gynecological surgery		Tsai MS et al. [55]
GI (Korea) (426)	95.30	Sedation-free colonoscopy	Older age, lower BMI and hysterectomy	Older age, lower BMI, Hysterectomy, diarrhea, 1st time colonoscopy and anxiety	Chung YW et al. [56]
GI (Japan) (848)	99.60	Sedation-free colonoscopy	Lower BMI, female, preparation status, previous hysterectomy	Lower BMI, younger age, intubation time, preparation status, previous hysterectomy	Takahashi Y et al. [57]
GI (Turkey) (120)	88	As needed sedation		Mean pain score: 2.0 for the nonsedated and 3.8 for the sedated patients ($P<0.05$).	Yörük G et al. [58]
GI (Japan) (259)	95.96	Water instillation vs air insufflations		17.1 % (water) and 33.3 (air) had abdominal pain ($P<0.001$)	Hamamoto N et al. [59]
GI (Italy) (124)		On demand sedation (66% required sedation)		34% reported moderate or severe pain and 22% unwilling to repeat	Terruzzi et al. [60]
GI (Greece) (173)	92 unsedated 87.9 success	On demand sedation		Male gender, segmental colonic resection predict success	Ladas et al. [61]
GI (Germany) (100)	95 (87 willing to repeat)	As needed sedation (5%)		On a scale of 1 to 9, barium enema and colonoscopy produced similar ratings of discomfort (3.1 vs 3.2)	Eckardt VF et al. [62]
Surgeons (Singapore) (40)	78 (93 willing to repeat)	As needed sedation	23% required intravenous sedation	30% had no pain, 55% minimal pain, 8% moderate pain and 3% severe pain	Seow-Choen F et al. [63]

intubation is pain although polyps and adenoma detection rate seems not to be affected by premedication.

Since a painful experience with colonoscopy may have a negative impact on patients' compliance and on the efficacy of screening and surveillance programs, proper sedation/analgesia may definitely exert a positive role in this setting, although many studies highlighted a number of variables affecting the probability of accepting and completing colonoscopy without pain, such as gender, age, BMI, and previous abdominal surgery (Table 1). On the other hand unsedated colonoscopy is widespread and well accepted throughout the world [53-63]. In a recent study [64] unsedated patients were able to complete the examination without any premedication in a high percentage of cases (85% of men, 67% of women) and 97.4% of them stated they would repeat the procedure without sedation. In this study patients who needed sedation were more likely to have a prolonged and/or incomplete procedure. A 2010 literature review [53] reported that unsedated colonoscopy is still practiced in many parts of the world.

The interest in this issue rises from the increased use of colonoscopy in colorectal cancer screening. This suggests a reassessment of sedation practice in order to lower costs and complication rate, reduce the need for post procedural monitoring, recovery time, nursing care and escort [65]. Not with standing these benefits, most patients undergoing colonoscopy prefer to be sedated for their examination.

A new trend in recent studies is to evaluate the effectiveness of warm water infusion or carbon dioxide insufflations instead of air in reducing the need for sedoanalgesia during colonoscopy [66-69].

As stated by Teruzzi and al. in their recent review [65]: "Unsedated

colonoscopy is fascinating for both physician and patients, although not for all. It is crucial to identify the subset of subject most likely to attempt and complete unsedated procedures, which could benefit from being offered one of the above options".

In conclusion, the variation in sedation practice from country to country reflects many different factors including the cost and availability of monitoring equipment and drugs and the lack of professional training on cardiopulmonary resuscitation.

In spite of cultural and social differences that exist from one country to another, economic considerations are the dominant forces affecting the implementation of sedation during gastrointestinal endoscopy.

References

- Heuss LT, Peter S. Propofol use by gastroenterologists-the European experience. *Gastrointest Endosc Clin N Am.* 2008; 18: 727-738.
- Chatman N, Sutherland JR, van der Zwan R, Abraham N. A survey of patient understanding and expectations of sedation/anaesthesia for colonoscopy. *Anaesth Intensive Care.* 2013; 41: 369-373.
- Heuss LT, Froehlich F, Beglinger C. Changing patterns of sedation and monitoring practice during endoscopy: results of a nationwide survey in Switzerland. *Endoscopy.* 2005; 37: 161-166.
- Cohen LB, Wechsler JS, Gaetano JN, Benson AA, Miller KM, Durkalski V, et al. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol.* 2006; 101: 967-974.
- Ladas SD, Aabakken L, Rey JF, Nowak A, Zakaria S, Adamonis K, et al. Use of sedation for routine diagnostic upper gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy Survey of National Endoscopy Society Members. *Digestion.* 2006; 74: 69-77.
- Benson AA, Cohen LB, Waye JD, Akhavan A, Aisenberg J. Endoscopic sedation in developing and developed countries. *Gut Liver.* 2008; 2: 105-112.

7. Baudet JS, Borque P, Borja E, Alarcón-Fernández O, Sánchez-del-Río A, Campo R, et al. Use of sedation in gastrointestinal endoscopy: a nationwide survey in Spain. *Eur J Gastroenterol Hepatol.* 2009; 21: 882-888.
8. Paspatis GA, Manolaraki MM, Tribonias G, Theodoropoulou A, Vardas E, Konstantinidis K, et al. Endoscopic sedation in Greece: results from a nationwide survey for the Hellenic Foundation of gastroenterology and nutrition. *Dig Liver Dis.* 2009; 41: 807-811.
9. Fanti L, Agostoni M, Gemma M, Radaelli F, Conigliaro R, Beretta L, et al. Sedation and monitoring for gastrointestinal endoscopy: A nationwide web survey in Italy. *Dig Liver Dis.* 2011; 43: 726-730.
10. SIED, SIAARTI, ANOTE. Linee Guida per la Sedazione in Endoscopia Digestiva. *Giorn Ital End Dig.* 2000; 23: 21.
11. Conigliaro R, Rossi A. Italian Society of Digestive Endoscopy (SIED) Sedation Commission . Implementation of sedation guidelines in clinical practice in Italy: results of a prospective longitudinal multicenter study. *Endoscopy.* 2006; 38: 1137-1143.
12. Nwokediuko SC, Obienu O. Sedation practices for routine diagnostic upper gastrointestinal endoscopy in Nigeria. *World J Gastrointest Endosc.* 2012; 4: 260-265.
13. Wang HL, Ye F, Liao WF, Xia B, Zheng GR. Unsedated versus sedated gastrointestinal endoscopy: a questionnaire investigation in Wuhan, central China. *J Huazhong Univ Sci Technolog Med Sci.* 2013; 33: 857-861.
14. Triantafyllidis JK, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. *World J Gastroenterol.* 2013; 19: 463-481.
15. Gasparovic S, Rustemovic N, Opacic M, Premuzic M, Korusic A, Bozиков J, et al. Clinical analysis of propofol deep sedation for 1,104 patients undergoing gastrointestinal endoscopic procedures: a three year prospective study. *World J Gastroenterol.* 2006; 12: 327-330.
16. Wehrmann T, Kokabpick S, Lembcke B, Caspary WF, Seifert H. Efficacy and safety of intravenous propofol sedation during routine ERCP: a prospective, controlled study. *Gastrointest Endosc.* 1999; 49: 677-683.
17. Garewal D, Powell S, Milan SJ, Nordmeyer J, Waikar P. Sedative techniques for endoscopic retrograde cholangiopancreatography. *Cochrane Database Syst Rev.* 2012; 6: 007274.
18. Qadeer MA, Vargo JJ, Khandwala F, Lopez R, Zuccaro G. Propofol versus traditional sedative agents for gastrointestinal endoscopy: a meta-analysis. *Clin Gastroenterol Hepatol.* 2005; 3: 1049-1056.
19. Rex DK, Deenadayalu VP, Eid E, Imperiale TF, Walker JA, Sandhu K, et al. Endoscopist-directed administration of propofol: a worldwide safety experience. *Gastroenterology.* 2009; 137: 1229-1237.
20. Riphaus A, Wehrmann T, Weber B, Arnold J, Beilenhoff U, Bitter H, et al. S3 Guideline: Sedation for gastrointestinal endoscopy 2008. *Endoscopy.* 2009; 41: 787-815.
21. Keats AS. The ASA classification of physical status--a recapitulation. *Anesthesiology.* 1978; 49: 233-236.
22. Enestvedt BK, Eisen GM, Holub J, Lieberman DA. Is the American Society of Anesthesiologists classification useful in risk stratification for endoscopic procedures? *Gastrointest Endosc.* 2013; 77: 464-471.
23. Vargo JJ, Cohen LB, Rex DK, Kwo PY. Position Statement: Non anesthesiologist administration of propofol for GI Endoscopy. *Gastrointest Endosc.* 2009; 70: 1053-1059.
24. Vargo JJ, Cohen LB, Rex DK, Kwo PY. Position Statement: Non anesthesiologist administration of propofol for GI Endoscopy. *Am J Gastroenterol.* 2009; 104: 2886-2892.
25. Vargo JJ, Cohen LB, Rex DK, Kwo PY. Position Statement: Non anesthesiologist administration of propofol for GI Endoscopy. *Gastroenterology.* 2009; 137: 216-217.
26. Vargo JJ, Cohen LB, Rex DK, Kwo PY. Position Statement: Non anesthesiologist administration of propofol for GI Endoscopy. *Hepatology.* 2009; 50:1683-1689.
27. Dumonceau JM, Riphaus A, Aparicio JR, Beilenhoff U, Knappe JT, Ortmann M, et al. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Guideline: Non-anesthesiologist administration of propofol for GI endoscopy. *Eur J Anaesthesiol.* 2010; 27: 1016-1030.
28. Dumonceau JM, Riphaus A, Aparicio JR, Beilenhoff U, Knappe JT, Ortmann M, et al. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Guideline: Non-anesthesiologist administration of propofol for GI endoscopy. *Endoscopy.* 2010; 42: 960-974.
29. Perel A. Non-anesthesiologists should not be allowed to administer propofol for procedural sedation: a Consensus Statement of 21 European National Societies of Anaesthesia. *Eur J Anaesthesiol.* 2011; 28: 580-584.
30. Pelosi P. Board of the European Society of Anaesthesiology. Retraction of endorsement: European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates and the European Society of Anaesthesiology Guideline--non-anesthesiologist administration of propofol for gastrointestinal endoscopy. *Eur J Anaesthesiol.* 2012; 29: 208.
31. Dumonceau JM, Riphaus A, Aparicio JR, Beilenhoff U, Ortmann M, Paspatis G, et al. Reply: Retraction of endorsement: European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates and the European Society of Anaesthesiology Guideline -- non-anesthesiologist administration of propofol for gastrointestinal endoscopy. *European Journal of Anaesthesiology.* 2012; 29: 208-219.
32. Dumonceau JM. Nonanesthesiologist administration of propofol: it's all about money. *Endoscopy.* 2012; 44: 453-455.
33. Werner C, Smith A, Van Aken H. Guidelines on non-anesthesiologist administration of propofol for gastrointestinal endoscopy: a double-edged sword. *Eur J Anaesthesiol.* 2011; 28: 553-555.
34. Vargo JJ, Mark H, DeLegge, Andrew D, Feld, Patrick D, Gerstenberger, Paul Y, Kwo, Jenifer R, Lightdale, et al. American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association Institute; American Society for Gastrointestinal Endoscopy; Society for Gastroenterology Nurses and Associates, Multisociety sedation curriculum for gastrointestinal endoscopy. *Gastroenterology.* 2012; 143:18-41.
35. Vargo JJ, DeLegge MH, Feld AD, Gerstenberger PD, Kwo PY, Lightdale JR, et al. Multisociety Sedation Curriculum for Gastrointestinal Endoscopy. *Am J Gastroenterol.* 2012.
36. American Association for Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association Institute; American Society for Gastrointestinal Endoscopy; Society for Gastroenterology Nurses and Associates, Vargo JJ, et al. Multisociety sedation curriculum for gastrointestinal endoscopy. *Gastrointest Endosc.* 2012; 76: 1-25.
37. Multisociety Sedation Curriculum for Gastrointestinal Endoscopy. *Hepatology.* 2012; 56: 1-25.
38. Multisociety sedation curriculum for gastrointestinal endoscopy. *Gastroenterol Nurs.* 2012; 35: 1-25.
39. Dumonceau JM, Riphaus A, Beilenhoff U, Vilmann P, Hornslet P, Aparicio JR, et al. European curriculum for sedation training in gastrointestinal endoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA). *Endoscopy.* 2013; 45: 496-504.
40. Verhagen CC, Niezink AG, Engels YY, Hekster YY, Doornebal JJ, Vissers KC. Off-label use of drugs in pain medicine and palliative care: an algorithm for the assessment of its safe and legal prescription. *Pain Pract.* 2008; 8: 157-163.
41. Aisenberg J, Cohen LB, Piorkowski JD. Propofol use under the direction of trained gastroenterologists: an analysis of the medicolegal implications. *Am J Gastroenterol.* 2007; 102: 707-713.
42. Axon AE. The use of propofol by gastroenterologists: medico-legal issues. *Digestion.* 2010; 82: 110-112.

43. McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. *Gastrointest Endosc.* 2008; 67: 910-923.
44. Froehlich F, Harris JK, Wietlisbach V, Burnand B, Vader JP, Gonvers JJ. EPAGE Study Group. Current sedation and monitoring practice for colonoscopy: an International Observational Study (EPAGE). *Endoscopy.* 2006; 38: 461-469.
45. Fisher NC, Bailey S, Gibson JA. A prospective, randomized controlled trial of sedation vs. no sedation in outpatient diagnostic upper gastrointestinal endoscopy. *Endoscopy.* 1998; 30: 21-24.
46. Campo R, Brullet E, Montserrat A, Calvet X, Moix J, Rué M, et al. Identification of factors that influence tolerance of upper gastrointestinal endoscopy. *Eur J Gastroenterol Hepatol.* 1999; 11: 201-204.
47. Campo R, Brullet E, Montserrat A, Calvet X, Rivero E, Brotons C. Topical pharyngeal anesthesia improves tolerance of upper gastrointestinal endoscopy: a randomized double-blind study. *Endoscopy.* 1995; 27:659- 664.
48. Evans LT, Saberi S, Kim HM, Elta GH, Schoenfeld P. Pharyngeal anesthesia during sedated EGDs: is "the spray" beneficial? A meta-analysis and systematic review. *Gastrointest Endosc.* 2006; 63: 761-766.
49. Kadayifci A, Parlar S, Aydinli M, Dag MS, Demir U, Savas MC. Unsedated transnasal versus conventional oral endoscopy in endoscopy naïve patients. *Acta Gastroenterol Belg.* 2014; 77: 224-228.
50. Rex DK. Does the use of sedation, or the level of sedation, affect detection during colonoscopy? *Am J Gastroenterol.* 2012; 107:1849-1851.
51. Radaelli F, Meucci G, SgROI G, Minoli G. Italian Association of Hospital Gastroenterologists (AIGO). Technical performance of colonoscopy: the key role of sedation/analgesia and other quality indicators. *Am J Gastroenterol.* 2008; 103: 1122-1130.
52. Bannert C, Reinhart K, Dunkler D, Trauner M, Renner F, Knoflach P, et al. Sedation in screening colonoscopy: impact on quality indicators and complications. *Am J Gastroenterol.* 2012; 107: 1837-1848.
53. Leung FW, Aljebreen AM, Brocchi E, Chang EB, Liao WC, Mizukami T, et al. Sedation-risk-free colonoscopy for minimizing the burden of colorectal cancer screening. *World J Gastrointest Endosc.* 2010; 2: 81-89.
54. Liao WC, Chiu HM, Chen CC, Lee YC, Wu MS, Lin JT, et al. A prospective evaluation of the feasibility of primary screening with unsedated colonoscopy. *Gastrointest Endosc.* 2009; 70: 724-731.
55. Tsai MS, Su YH, Liang JT, Lai HS, Lee PH. Patient factors predicting the completion of sedation-free colonoscopy. *Hepatogastroenterology.* 2008; 55: 1606-1608.
56. Chung YW, Han DS, Yoo KS, Park CK. Patient factors predictive of pain and difficulty during sedation-free colonoscopy: a prospective study in Korea. *Dig Liver Dis.* 2007; 39: 872-876.
57. Takahashi Y, Tanaka H, Kinjo M, Sakumoto K. Prospective evaluation of factors predicting difficulty and pain during sedation-free colonoscopy. *Dis Colon Rectum.* 2005; 48: 1295-1300.
58. Yoruk G, Aksoz K, Unsal B, Buyrac Z, Buran T, Yazicioglu N. Colonoscopy without sedation. *Turk J Gastroenterol.* 2003; 14: 59-63.
59. Hamamoto N, Nakanishi Y, Morimoto N, Inoue H, Tatukawa M, Nakata S, et al. A new water instillation method for colonoscopy without sedation as performed by endoscopists-in-training. *Gastrointest Endosc.* 2002; 56: 825-828.
60. Terruzzi V, Meucci G, Radaelli F, Terreni N, Minoli G. Routine versus "on demand" sedation and analgesia for colonoscopy: a prospective randomized controlled trial. *Gastrointest Endosc.* 2001; 54: 169-174.
61. Ladas SD. Factors predicting the possibility of conducting colonoscopy without sedation. *Endoscopy.* 2000; 32: 688-692.
62. Eckardt VF, Kanzler G, Willems D, Eckardt AJ, Bernhard G. Colonoscopy without premedication versus barium enema: a comparison of patient discomfort. *Gastrointest Endosc.* 1996; 44: 177-180.
63. Seow-Choen F, Leong AF, Tsang C. Selective sedation for colonoscopy. *Gastrointest Endosc.* 1994; 40: 661-664.
64. Petrini JL, Egan JV, Hahn WV. Unsedated colonoscopy: patient characteristics and satisfaction in a community-based endoscopy unit. *Gastrointest Endosc.* 2009; 69: 567-572.
65. Terruzzi V, Paggi S, Amato A, Radaelli F. Unsedated colonoscopy: A neverending story. *World J Gastrointest Endosc.* 2012; 4: 137-141.
66. Brocchi E, Pezzilli R, Tomassetti P, Campana D, Morselli-Labate AM, Corinaldesi R. Warm water or oil-assisted colonoscopy: toward simpler examinations? *Am J Gastroenterol.* 2008; 103: 581-587.
67. Amato A, Radaelli F, Paggi S, Baccarin A, Spinzi G, Terruzzi V. Carbon dioxide insufflation or warm-water infusion versus standard air insufflation for unsedated colonoscopy: a randomized controlled trial. *Dis Colon Rectum.* 2013; 56: 511-518.
68. Rabenstein T, Radaelli F, Zolk O. Warm water infusion colonoscopy: a review and meta-analysis. *Endoscopy.* 2012; 44: 940-951.
69. Trevisani L, Zelante A, Sartori S. Colonoscopy, pain and fears: Is it an indissoluble trinomial? *World J Gastrointest Endosc.* 2014; 6: 227-233.