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**Sedation in gastrointestinal endoscopy: Where are we at in 2014?**

Ferreira AO *et al.* Sedation in gastrointestinal endoscopy

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**Abstract**

Gastrointestinal endoscopies are invasive and unpleasant procedures that are increasingly being used worldwide. The importance of high quality procedures (especially in colorectal cancer screening), the increasing patient awareness and the expectation of painless examination, increase the need for procedural sedation. The best single sedation agent for endoscopy is propofol which, due to its’ pharmacokinetic/dynamic profile allows for a higher patient satisfaction and procedural quality and lower induction and recovery times, while maintaining the safety of traditional sedation. Propofol is an anesthetic agent when used in higher doses than those needed for endoscopy. Because of this important feature it may lead to cardiovascular and respiratory depression and, ultimately, to cardiac arrest and death. Fueled by this argument, concern over the safety of its administration by personnel without general anesthesia training has arisen. Propofol usage seems to be increasing but it’s still underused. It is a safe alternative for simple endoscopic procedures in low risk patients even if administered by non-anesthesiologists. Evidence on propofol safety in complex procedures and high risk patients is less robust and in these cases, the presence of an anesthetist should be considered. We review the existing evidence on the topic and evaluate the regional differences on sedation practices.

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**Key words:** Hypnotics and sedatives; Propofol; Conscious sedation; Endoscopy; Gastrointestinal

**Core tip:** Sedation in endoscopy is a hot topic. There is a wide range of practices depending on the countries and even regionally at a national level. These differences range from no sedation to traditional sedation or propofol based sedation (with or without an anesthetist) and are the result of several factors which include cultural aspects, medical training, legal responsibility and societal lobbying.Herein we review the most important evidence regarding the sedation aspects in the endoscopy suite and compare practices which vary among several countries.

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**INTRODUCTION**

Sedation is a fundamental aspect of gastrointestinal (GI) endoscopy. Although some patients can perform diagnostic esophagogastroduodenoscopy (EGD) and colonoscopy without sedation, the use of sedation is associated with a higher patient satisfaction[[1](#_ENREF_1),[2](#_ENREF_2)] and procedural quality[[3](#_ENREF_3)]. There is also an increasing demand for sedation by the patients and all endoscopists should be in position to comply with such demand.

There are several options for sedation which range from light sedation (anxiolysis) to general anesthesia depending on the procedure being performed, the center expertise and the individual patient. Still, the most commonly used sedation is moderate-deep sedation achieved by midazolam with or without an opioid (meperidine/pethidine, fentanyl or alfentanyl), which is commonly designated as “traditional sedation”, with the other option being propofol which can also be used alone or in combination with analgesic opioids or midazolam. This review revolves around the value of sedation, the most common options and the similarities and differences between them. We also aim to discuss the role of anesthesia providers in the equation.

**SEDATION AND PHARMACOLOGY**

Midazolam is a short acting, water soluble, highly lipophilic benzodiazepine that was approved in the 80’s. The agents of this class act by binding to the type A γ-aminobutyric acid (GABA) receptor and enhancing its’ inhibitory actions on the central nervous system. Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and antegrade amnestic properties[[4](#_ENREF_4)]. It’s 1.5 - 3.5 times more potent than diazepam and it has a shorter onset (1-2 min) and duration of action (15-80 min) when compared to other benzodiazepines[[5](#_ENREF_5),[6](#_ENREF_6)]. Midazolam is metabolized by the liver and its’ metabolites are excreted by the kidney.

Intravenous midazolam allows for moderate (conscious) sedation with commonly used doses in endoscopy ranging from 2 mg to 6 mg[[7](#_ENREF_7)] but frequently a state of deep sedation is inadvertently achieved, at least when used in combination with an opioid[[8](#_ENREF_8)].

The major side effect is respiratory depression but it may also cause cardiovascular effects (hypotension and dysrhythmias) and occasionally “paradoxical” reactions occur with hostility and aggression occurring after administration. This reaction has been described to have an incidence of 1.4% and while it usually doesn’t preclude completion of the procedure it renders it more difficult. The combination of pethidine has been suggested, in an observational study, to lower the risk for such reactions[[9](#_ENREF_9)].

Midazolam action can be reversed by the administration of flumazenil (a benzodiazepine antagonist) which has an onset of action of 1-2 min with a duration of 60 min, a little shorter than midazolam explaining why the sedation level may deepen again after some time.

Propofol (2, 6-diisopropofol) is a hypnotic drug with minimal analgesic properties. Propofol also exerts its effect through potentiation of the GABA by reducing the rate of GABA-receptor dissociation[[10](#_ENREF_10)].

It is highly lipophilic which enables it to have a quick onset, corresponding to one arm-brain circulation time (30-45 s) and a short, predictable duration of action (4-8 min)[[11](#_ENREF_11)]. Propofol is metabolized in the liver and excreted by the kidney. Several factors significantly alter its’ pharmacokinetic profile and clinical effects with the major ones being age, weight and sex, with the elderly being significantly more sensitive to low doses.

Propofol formulations vary but usually they contain soybean oil and purified egg phosphatide and it should be avoided in patients with known allergies/hypersensitivity to egg and soy products.

Propofol induces respiratory depression in a dose-response fashion and it has a negative cardiac inotropic effect causing a decrease in cardiac output, systemic vascular resistance and arterial pressure[[7](#_ENREF_7)]. Transient pain on injection site is common, affecting up to 50% of patients[[12](#_ENREF_12)]. Apart from these clinically non-significant effects, serious adverse events leading to death are very rare and the risk is estimated to be even slimmer in low risk patients (ASA I-II), ranging from 1:10000 to 1:300000[[13](#_ENREF_13)].

The most common agents used for sedation and their pharmacologic profile are shown in Table 1.

**HISTORICAL AND GLOBAL PERSPECTIVE**

GI endoscopies are invasive, unpleasant and sometimes painful experiences. To overcome such unpleasantness, we have been searching for ways to minimize it since the introduction of the fiberscope in the 50’s.

The technological advances in endoscopy have improved the diagnostic and therapeutic capabilities throughout the GI tract but they have also allowed for faster and less painful examinations. Advances like the utilization of thinner endoscopes[[14](#_ENREF_14)], variable stiffness colonoscopes[[15](#_ENREF_15)], CO2 insufflation[[16](#_ENREF_16)] and water immersion techniques (in colonoscopy)[[17](#_ENREF_17)] allow for less painful procedures. Although helpful, these options are probably not as effective as medical sedation has been shown to be.

There has been a continuous evolution on sedation practices for endoscopy since the early 60’s when pentobarbital use was described in conjunction with a transtracheal xylocaine injection[[18](#_ENREF_18)]. The use of meperidine as an analgesic was an initial strategy and it was followed by the widespread adoption of the combination with diazepam, which was shown to improve the rate of “satisfactory examinations” by 20% comparing to meperidine alone[[19](#_ENREF_19)]. This set the *rationale* for the so called traditional sedation.

After almost two decades there was the advent of midazolam[[6](#_ENREF_6)]. Midazolam had a very good acceptance in the endoscopy community in virtue of its faster induction time, higher effectiveness and shorter duration of action comparing to diazepam while keeping the safety feeling provided by the existence of a reversal agent. However, there were several (71) death reports in the 80’s with midazolam based sedation and the Food and Drug Administration (FDA) issued a warning on this topic. Later, a more systematic epidemiological approach, led by a joint effort from the FDA and the American Society of Gastrointestinal Endoscopy (ASGE), failed to show an increased risk of death with midazolam compared with diazepam[[20](#_ENREF_20)]. At the present time, midazolam is considered a safe agent and is commonly used as a sedative in gastrointestinal endoscopy.

Propofol, an ultra-short acting hypnotic agent, entered the arena a few years after midazolam[[12](#_ENREF_12)] but it had a much slower uptake due to its use mostly as an anesthetic agent and as a sedative for critically ill patients and its’ product label states that it “should be administered by persons with training in general anesthesia” in the United States and by anesthetists and intensive care physicians in some European countries. Because of this, most endoscopists feel untrained to administer propofol. Still, from a pharmacokinetic/pharmacodynamic point of view, propofol is superior to midazolam as it has a faster onset and a shorter predictable duration of action[[11](#_ENREF_11)]. Propofol has since been proved to be a better sedative for endoscopy when compared to traditional sedation, improving both patient and endoscopist satisfaction, procedural quality indicators (such as cecal intubation time), induction, wake up and psychomotor recovery times[[1](#_ENREF_1),[2](#_ENREF_2),[21-23](#_ENREF_21)]. These improvements are achieved without an increased risk for adverse events as shown in several meta-analyses of randomized controlled trials (RCT)[[1](#_ENREF_1),[2](#_ENREF_2),[24](#_ENREF_24)]. These characteristics may have significant impact in procedural quality, patients’ acceptance (especially for screening procedures) and endoscopic unit productivity.

One important concern regarding sedation in colonoscopy is the theoretical increase in perforation risk. In two observational but robust population based studies in the United States it has been shown that propofol sedation is not associated with an increased perforation risk[[25](#_ENREF_25),[26](#_ENREF_26)]. It may, however, be associated with a slightly higher risk for aspiration pneumonia[[26](#_ENREF_26)]. Another recent observation study showed an increased risk for perforation but only in therapeutic colonoscopy and when adjusted for confounders the odds ratio was 1.34 with a *P* value of 0.04[[27](#_ENREF_27)]. Obviously, it is hard to detect small effect sizes for rare outcomes such as colonic perforation, but so far, the available evidence suggest that sedation doesn’t play a significant role in perforation rates.

Despite the advantages of propofol and the endorsement of propofol sedation by several national and international societies[[28-32](#_ENREF_28)], it is still underused in most settings, because of medico-legal aspects, namely the requirement of an anesthesiologist and, consequently, increased costs[[33](#_ENREF_33)].

The non-availability of NAAP seems to be a limiting step for the availability of propofol sedation and it significantly increases costs in a non-reasonable tradeoff. This has been shown in a recent cost-effectiveness analysis by Cesare Hassan, with a calculated cost of 1.5 million USD/life year gained[[34](#_ENREF_34)].

There is wide variability in sedation practice worldwide. In the United States the number of endoscopic procedures in increasing[[35](#_ENREF_35)], as a result of the increased uptake of colorectal cancer screening colonoscopy. The participation of an anesthesiologist in endoscopy has doubled from 14% in 2003 to 30% in 2009[[36](#_ENREF_36)] and it’s expected to pass the 50% mark by 2015[[37](#_ENREF_37)]. On the other hand, non-anesthesiologist administration of propofol (NAAP) is becoming less common, as a result of Medicare reimbursement change in 2009[[38](#_ENREF_38)], although this policy has been rejected by several states.

In Europe the variability is even bigger. In most countries routine diagnostic EGDs are performed without sedation[[39](#_ENREF_39)] with colonoscopies being more likely to receive some form of sedation[[33](#_ENREF_33)]. The countries with highest rates of propofol sedation are probably Switzerland[[40](#_ENREF_40)] and Germany[[41](#_ENREF_41)] with high rates of NAAP. In the latter, over 90% of the colonoscopies are performed with sedation, 97% of them with propofol and only 2% of those with support of an anesthesiologist. These data were acquired from a German national survey in 2011 with 732 respondents and showed an increase in sedation and propofol rates comparing to the first survey, 4 years earlier.

NAAP is also a common practice in Denmark, Austria, Spain, Italy, Greece, the Netherlands and Sweden[[32](#_ENREF_32),[42-45](#_ENREF_42)].

In other countries, like France and Portugal, virtually all endoscopic sedation with propofol is performed with an anesthesiologist. Unpublished data from our group regarding a national survey performed in Portugal in 2014, showed less than 3% of endoscopists perform NAAP and that propofol is used in less than half of the colonoscopies.

**SEDATION IN SPECIAL POPULATIONS**

There are populations that require specific considerations[[46](#_ENREF_46)], especially the elderly, the obese, patients with cirrhosis, pregnant women, patients with pulmonary disease and acutely ill patients.

In the elderly one must be aware of the slower onset of sedation and the higher sensitivity to sedatives. These patients are at an increased risk for cardiopulmonary events and aspiration syndrome. The recovery times are also increased due to slower hepatic and renal clearance and a higher fat body mass. Sedatives should be titrated at a slower pace and smaller doses should be generally used[[47](#_ENREF_47)].

Obesity is a growing pandemic, especially in the USA. Obesity is frequently associated with other comorbidities and is considered an independent risk factor hypoxemia and the need for airway permeabilization maneuvers[[48](#_ENREF_48)]. Still, even though these patients are at a higher risk for minor events, it’s considered safe to perform sedation for endoscopic procedures by trained personnel[[46](#_ENREF_46)].

Cirrhosis is a comorbid condition with significant impact on a patient’s health status. Cirrhotic patients are supposed to undergo surveillance EGDs for esophageal varices and frequently undergo endoscopic procedures for indications such as anemia, bleeding, liver transplant evaluation or adenoma surveillance. Sedation in these patients pose some concerns due to hepatic dysfunction, decreased drug clearance and risk for hepatic encephalopathy. Several studies looked into this effect. Riphaus *et al*[[49](#_ENREF_49)] performed a RCT that showed that propofol sedation was superior to midazolam in terms of recovery times and cognitive impairment after EGD[[49](#_ENREF_49)]. A larger RCT comprising 211 patients confirmed these findings[[50](#_ENREF_50)]. In a more recent RCT, in South Korea, propofol was shown to be safe in cirrhotic patients comparing to healthy controls[[51](#_ENREF_51)]. Propofol is, therefore, considered the best option for sedation in patients with cirrhosis.

Pregnant women seldom need endoscopic procedures and common sense dictates that elective procedures should be postponed if possible. However, in some instances endoscopy has to be performed. While sedation is considered safe for the woman, there isn’t high quality evidence to confirm it and some considerations have to made because of the possible risks to the fetus and are discussed in a ASGE guideline[[52](#_ENREF_52)]. Among narcotics, meperidine is the favored agent. Benzodiazepines are classified as FDA pregnancy class D and are best avoided. Propofol is class B and may be used during pregnancy and preferably by an anesthesiologist. All agents are best avoided during the first trimester due to higher theoretical risks to the fetus. During lactation propofol and fentanyl are considered safe options with no need to withhold breastfeeding.

Acutely ill or decompensated patients are best managed by an anesthesiologist and most guidelines recommend considering anesthesiologist support for ASA ≥ III patients, since most evidence on NAAP is on low risk patients and death have been reported only in ASA ≥III patients[[44](#_ENREF_44)].

**EVIDENCE**

There is high quality evidence comparing propofol to traditional sedation, which includes several RCTs and five systematic reviews (4 of them with meta-analysis - Table 2)[[1](#_ENREF_1),[2](#_ENREF_2),[21](#_ENREF_21),[23](#_ENREF_23),[24](#_ENREF_24)]. The results are very consistent in showing a similar rate of adverse events with propofol versus traditional sedation. The advantages of propofol are shorter recovery and discharge periods, higher post-anesthesia recovery scores, better sedation, and greater patient cooperation. One limitation of the majority of the RCTs included in the meta-analysis is the lack of anesthesiologist participation. This may limit the generalizability of the data but it’s unlikely that there would be a decrease in the safety or quality of this sedation when performed by an anesthesiologist.

The big question is therefore who should be responsible for the administration of propofol[[53](#_ENREF_53)].

To address this issue there is only one RCT[[54](#_ENREF_54)]. This study by Poincloux *et al*[54] randomized 90 low risk patients undergoing colonoscopy for sedation by anesthesiologist using a target control infusion (TCI) or by the endoscopist using a modified patient controlled sedation pedal. In this study patients who were sedated by anesthesiologists had more frequent side events (16% *vs* 3%; *P* = 0.008), had higher doses of propofol (94mg *vs* 260 mg), less pain but similar satisfaction levels.

Currently, we are performing a non-inferiority randomized trial addressing the safety of NAAP by comparing it no anesthesiologist sedation in low risk patients (ClinicalTrials.gov - NCT02067065). The interim analysis (100 patients) did not show a significant difference in the incidence of adverse events (primary endpoint) between the two groups (ref).

Apart from randomized controlled trials, there’s significant experience with NAAP and extensive prospective evaluation on the safety and effectiveness of this type of sedation, especially for low risk patients. Rex *et al*[38] published in 2009 a sum of all published evidence on NAAP and collected unpublished prospective and retrospective records from several centers all around the world, totaling 646080 cases out of which 4 patients died and 11 were intubated. These numbers are not very different from published mortality rates for general anesthesia which is 1:13322 (overall) and 1:200200 in ASA I-II[[13](#_ENREF_13)]. Recently, a large German experience of 24 441 cases on propofol and propofol with midazolam has been published[[55](#_ENREF_55)]. The data was collected prospectively and severe adverse events were reported in only 4 patients, with no severe outcomes (death or permanent neurologic damage).

With such a track record it will be very difficult to design a RCT powered to detect a difference in mortality or even in the need for endotracheal intubation (EOT). If we consider a probability of 1:20000 for EOT (3 times higher than published by Rex), then we would need a sample size of 17 133802 patients to exclude a 20% difference (of the expected incidence) between the groups with a confidence of 90% and a one-sided confidence interval of 95%.

**COST-EFFECTIVENESS**

In the study by Hassan *et al*[[34](#_ENREF_34)], the authors calculated the costs of training of nurses for EDP and assuming the published mortality rate of 0.0008% for EDP-colonoscopy and 0% for anesthesiologist sedation they concluded that the incremental cost-effectiveness ratio was 1.5 million USD/life year gained in the United States, 31 times above the accepted value of $50000 USD. This means that to make it cost effective a reduction in anesthesiologist reimbursement (for Medicare) from $95 to $6 would have to take place.

This study is based on the assumption that the presence of an anesthesiologist is 100% effective in avoiding death in these procedures.

**GUIDELINES**

As a consequence of the advantages provided by propofol sedation and the difficulty in adopting its use due to logistical, financial and medico-legal issues, several national and international guidelines have been published in the last decade and are shown in Table 3[[28-32](#_ENREF_28),[45](#_ENREF_45),[56](#_ENREF_56),[57](#_ENREF_57)]. These guidelines help to provide the framework to allow endoscopists to perform NAAP in their countries.

Of note, the German guidelines were the result of a collaboration between the GI endoscopy and anesthesia national societies and are therefore a valuable evidence based consensus document made by the country that has the highest level of propofol sedation in endoscopy in the world.

An interesting aspect is what occurred with the ESGE/ESGENA guideline. This one was also a joint effort with the European Society of Anesthesia (ESA) and was published in the November 2010 with the ESA support in both Endoscopy[[29](#_ENREF_29)] and the European Journal of Anesthesiology[[58](#_ENREF_58)]. Following this guideline, several national Anesthesiology societies declared to be against such endorsement and that position as was made public in a “Special Article” in the *ESA* journal in June 2011 by Perel[[59](#_ENREF_59)] and undersigned by 21 national societies. The argument used was the concern for patient safety based on the manufacturer’s package insert that states that “DIPRIVAN Injectable Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure“. As a consequence of this pressure there was a vote at the ESA General Assembly to retract the support of the ESA for the guideline that had been previously evaluated and approved by the ESA guidelines committee and Board of Directors. As of April 2012, without significant new evidence to support the change, or any kind of review of the same evidence, the ESA retracted the support[[60](#_ENREF_60)].

**CONCLUSION**

Propofol is currently considered the best candidate drug for sedation in endoscopic procedures. Still, we are in need for well-designed randomized clinical trials (with meaningful primary endpoints) to provide the definite proof of safety comparing to traditional sedation when used by non-anesthesiologists.

This kind of high quality evidence will help the different professional societies to overcome their differences and determine a robust, evidence-based, approach for safe and cost-effective sedation and monitoring in endoscopy.

**REFERENCES**

1 **Wang D**, Chen C, Chen J, Xu Y, Wang L, Zhu Z, Deng D, Chen J, Long A, Tang D, Liu J. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. *PLoS One* 2013; **8**: e53311 [PMID: 23308191 DOI: 10.1371/journal.pone.0053311]

2 **Singh H**, Poluha W, Cheung M, Choptain N, Baron KI, Taback SP. Propofol for sedation during colonoscopy. *Cochrane Database Syst Rev* 2008; **(4)**: CD006268 [PMID: 18843709 DOI: 10.1002/14651858.CD006268.pub2]

3 **Bannert C**, Reinhart K, Dunkler D, Trauner M, Renner F, Knoflach P, Ferlitsch A, Weiss W, Ferlitsch M. Sedation in screening colonoscopy: impact on quality indicators and complications. *Am J Gastroenterol* 2012; **107**: 1837-1848 [PMID: 23147522 DOI: 10.1038/ajg.2012.347]

4 **Reves JG**, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology* 1985; **62**: 310-324 [PMID: 3156545]

5 **Kanto JH**. Midazolam: the first water-soluble benzodiazepine. Pharmacology, pharmacokinetics and efficacy in insomnia and anesthesia. *Pharmacotherapy* 1985; **5**: 138-155 [PMID: 3161005]

6 **Cole SG**, Brozinsky S, Isenberg JI. Midazolam, a new more potent benzodiazepine, compared with diazepam: a randomized, double-blind study of preendoscopic sedatives. *Gastrointest Endosc* 1983; **29**: 219-222 [PMID: 6618119]

7 **Cohen LB**, Delegge MH, Aisenberg J, Brill JV, Inadomi JM, Kochman ML, Piorkowski JD. AGA Institute review of endoscopic sedation. *Gastroenterology* 2007; **133**: 675-701 [PMID: 17681185 DOI: 10.1053/j.gastro.2007.06.002]

8 **Patel S**, Vargo JJ, Khandwala F, Lopez R, Trolli P, Dumot JA, Conwell DL, Zuccaro G. Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. *Am J Gastroenterol* 2005; **100**: 2689-2695 [PMID: 16393221 DOI: 10.1111/j.1572-0241.2005.00320.x]

9 **Tae CH**, Kang KJ, Min BH, Ahn JH, Kim S, Lee JH, Rhee PL, Kim JJ. Paradoxical reaction to midazolam in patients undergoing endoscopy under sedation: Incidence, risk factors and the effect of flumazenil. *Dig Liver Dis* 2014; **46**: 710-715 [PMID: 24893689 DOI: 10.1016/j.dld.2014.04.007]

10 **Hara M**, Kai Y, Ikemoto Y. Propofol activates GABAA receptor-chloride ionophore complex in dissociated hippocampal pyramidal neurons of the rat. *Anesthesiology* 1993; **79**: 781-788 [PMID: 8214758]

11 **Kanto J**, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clin Pharmacokinet* 1989; **17**: 308-326 [PMID: 2684471 DOI: 10.2165/00003088-198917050-00002]

12 **Gepts E**, Claeys MA, Camu F, Smekens L. Infusion of propofol ('Diprivan') as sedative technique for colonoscopies. *Postgrad Med J* 1985; **61** Suppl 3: 120-126 [PMID: 3877279]

13 **Lagasse RS**. Anesthesia safety: model or myth? A review of the published literature and analysis of current original data. *Anesthesiology* 2002; **97**: 1609-1617 [PMID: 12459692]

14 **Töx U**, Schumacher B, Toermer T, Terheggen G, Mertens J, Holzapfel B, Lehmacher W, Goeser T, Neuhaus H. Propofol sedation for colonoscopy with a new ultrathin or a standard endoscope: a prospective randomized controlled study. *Endoscopy* 2013; **45**: 439-444 [PMID: 23468196 DOI: 10.1055/s-0032-1326270]

15 **Othman MO**, Bradley AG, Choudhary A, Hoffman RM, Roy PK. Variable stiffness colonoscope versus regular adult colonoscope: meta-analysis of randomized controlled trials. *Endoscopy* 2009; **41**: 17-24 [PMID: 19160154 DOI: 10.1055/s-0028-1103488]

16 **Wu J**, Hu B. The role of carbon dioxide insufflation in colonoscopy: a systematic review and meta-analysis. *Endoscopy* 2012; **44**: 128-136 [PMID: 22271023 DOI: 10.1055/s-0031-1291487]

17 **Leung FW**, Amato A, Ell C, Friedland S, Harker JO, Hsieh YH, Leung JW, Mann SK, Paggi S, Pohl J, Radaelli F, Ramirez FC, Siao-Salera R, Terruzzi V. Water-aided colonoscopy: a systematic review. *Gastrointest Endosc* 2012; **76**: 657-666 [PMID: 22898423 DOI: 10.1016/j.gie.2012.04.467]

18 **Firth JD**. An anesthetic technique for oral endoscopy. *Anesth Analg* 1960; **39**: 175-179 [PMID: 13823052]

19 **Ticktin HE**, Trujillo NP. Evaluation of diazepam for pre-endoscopy medication. *Am J Dig Dis* 1965; **10**: 979-984 [PMID: 5846505]

20 **Arrowsmith JB**, Gerstman BB, Fleischer DE, Benjamin SB. Results from the American Society for Gastrointestinal Endoscopy/U.S. Food and Drug Administration collaborative study on complication rates and drug use during gastrointestinal endoscopy. *Gastrointest Endosc* 1991; **37**: 421-427 [PMID: 1833259]

21 **Bo LL**, Bai Y, Bian JJ, Wen PS, Li JB, Deng XM. Propofol vs traditional sedative agents for endoscopic retrograde cholangiopancreatography: a meta-analysis. *World J Gastroenterol* 2011; **17**: 3538-3543 [PMID: 21941422 DOI: 10.3748/wjg.v17.i30.3538]

22 **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 [PMID: 18440381 DOI: 10.1016/j.gie.2007.12.046]

23 **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 [PMID: 16271333]

24 **Garewal D**, Powell S, Milan SJ, Nordmeyer J, Waikar P. Sedative techniques for endoscopic retrograde cholangiopancreatography. *Cochrane Database Syst Rev* 2012; **6**: CD007274 [PMID: 22696368 DOI: 10.1002/14651858.CD007274.pub2]

25 **Bielawska B**, Day AG, Lieberman DA, Hookey LC. Risk factors for early colonoscopic perforation include non-gastroenterologist endoscopists: a multivariable analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 85-92 [PMID: 23891916 DOI: 10.1016/j.cgh.2013.06.030]

26 **Cooper GS**, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. *JAMA Intern Med* 2013; **173**: 551-556 [PMID: 23478904 DOI: 10.1001/jamainternmed.2013.2908]

27 **Adeyemo A**, Bannazadeh M, Riggs T, Shellnut J, Barkel D, Wasvary H. Does sedation type affect colonoscopy perforation rates? *Dis Colon Rectum* 2014; **57**: 110-114 [PMID: 24316954 DOI: 10.1097/dcr.0000000000000002]

28 **Vargo JJ**, DeLegge MH, Feld AD, Gerstenberger PD, Kwo PY, Lightdale JR, Nuccio S, Rex DK, Schiller LR. Multisociety sedation curriculum for gastrointestinal endoscopy. *Gastroenterology* 2012; **143**: e18-e41 [PMID: 22624720 DOI: 10.1053/j.gastro.2012.05.001]

29 **Dumonceau JM**, Riphaus A, Aparicio JR, Beilenhoff U, Knape JT, Ortmann M, Paspatis G, Ponsioen CY, Racz I, Schreiber F, Vilmann P, Wehrmann T, Wientjes C, Walder B. 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 [PMID: 21072716 DOI: 10.1055/s-0030-1255728]

30 **Riphaus A**, Wehrmann T, Weber B, Arnold J, Beilenhoff U, Bitter H, von Delius S, Domagk D, Ehlers AF, Faiss S, Hartmann D, Heinrichs W, Hermans ML, Hofmann C, In der Smitten S, Jung M, Kähler G, Kraus M, Martin J, Meining A, Radke J, Rösch T, Seifert H, Sieg A, Wigginghaus B, Kopp I. [S3-guidelines--sedation in gastrointestinal endoscopy]. *Z Gastroenterol* 2008; **46**: 1298-1330 [PMID: 19012203 DOI: 10.1055/s-2008-1027850]

31 **Byrne MF**, Chiba N, Singh H, Sadowski DC. Propofol use for sedation during endoscopy in adults: a Canadian Association of Gastroenterology position statement. *Can J Gastroenterol* 2008; **22**: 457-459 [PMID: 18478130]

32 **Schreiber F**. Austrian Society of Gastroenterology and Hepatology (OGGH)--guidelines on sedation and monitoring during gastrointestinal endoscopy. *Endoscopy* 2007; **39**: 259-262 [PMID: 17385114 DOI: 10.1055/s-2007-966254]

33 **Riphaus A**, Macias-Gomez C, Devière J, Dumonceau JM. Propofol, the preferred sedation for screening colonoscopy, is underused. Results of an international survey. *Dig Liver Dis* 2012; **44**: 389-392 [PMID: 22119619 DOI: 10.1016/j.dld.2011.10.019]

34 **Hassan C**, Rex DK, Cooper GS, Benamouzig R. Endoscopist-directed propofol administration versus anesthesiologist assistance for colorectal cancer screening: a cost-effectiveness analysis. *Endoscopy* 2012; **44**: 456-464 [PMID: 22531982 DOI: 10.1055/s-0032-1308936]

35 **Cohen LB**, Wecsler JS, Gaetano JN, Benson AA, Miller KM, Durkalski V, Aisenberg J. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol* 2006; **101**: 967-974 [PMID: 16573781 DOI: 10.1111/j.1572-0241.2006.00500.x]

36 **Liu H**, Waxman DA, Main R, Mattke S. Utilization of anesthesia services during outpatient endoscopies and colonoscopies and associated spending in 2003-2009. *JAMA* 2012; **307**: 1178-1184 [PMID: 22436958 DOI: 10.1001/jama.2012.270]

37 **Inadomi JM**, Gunnarsson CL, Rizzo JA, Fang H. Projected increased growth rate of anesthesia professional-delivered sedation for colonoscopy and EGD in the United States: 2009 to 2015. *Gastrointest Endosc* 2010; **72**: 580-586 [PMID: 20630511 DOI: 10.1016/j.gie.2010.04.040]

38 **Rex DK**. Effect of the Centers for Medicare & amp; Medicaid Services policy about deep sedation on use of propofol. *Ann Intern Med* 2011; **154**: 622-626 [PMID: 21536938 DOI: 10.7326/0003-4819-154-9-201105030-00007]

39 **Ladas SD**, Aabakken L, Rey JF, Nowak A, Zakaria S, Adamonis K, Amrani N, Bergman JJ, Boix Valverde J, Boyacioglu S, Cremers I, Crowe J, Deprez P, Díte P, Eisen M, Eliakim R, Fedorov ED, Galkova Z, Gyokeres T, Heuss LT, Husic-Selimovic A, Khediri F, Kuznetsov K, Marek T, Munoz-Navas M, Napoleon B, Niemela S, Pascu O, Perisic N, Pulanic R, Ricci E, Schreiber F, Svendsen LB, Sweidan W, Sylvan A, Teague R, Tryfonos M, Urbain D, Weber J, Zavoral M. 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 [PMID: 17135728 DOI: 10.1159/000097466]

40 **Heuss LT**, Froehlich F, Beglinger C. Nonanesthesiologist-administered propofol sedation: from the exception to standard practice. Sedation and monitoring trends over 20 years. *Endoscopy* 2012; **44**: 504-511 [PMID: 22389232 DOI: 10.1055/s-0031-1291668]

41 **Riphaus A**, Geist F, Wehrmann T. Endoscopic sedation and monitoring practice in Germany: re-evaluation from the first nationwide survey 3 years after the implementation of an evidence and consent based national guideline. *Z Gastroenterol* 2013; **51**: 1082-1088 [PMID: 24022202 DOI: 10.1055/s-0033-1335104]

42 **Slagelse C**, Vilmann P, Hornslet P, Hammering A, Mantoni T. Nurse-administered propofol sedation for gastrointestinal endoscopic procedures: first Nordic results from implementation of a structured training program. *Scand J Gastroenterol* 2011; **46**: 1503-1509 [PMID: 22050137 DOI: 10.3109/00365521.2011.619274]

43 **Paspatis GA**, Manolaraki MM, Tribonias G, Theodoropoulou A, Vardas E, Konstantinidis K, Chlouverakis G, Karamanolis DG. Endoscopic sedation in Greece: results from a nationwide survey for the Hellenic Foundation of gastroenterology and nutrition. *Dig Liver Dis* 2009; **41**: 807-811 [PMID: 19410522 DOI: 10.1016/j.dld.2009.03.003]

44 **Rex DK**, Deenadayalu VP, Eid E, Imperiale TF, Walker JA, Sandhu K, Clarke AC, Hillman LC, Horiuchi A, Cohen LB, Heuss LT, Peter S, Beglinger C, Sinnott JA, Welton T, Rofail M, Subei I, Sleven R, Jordan P, Goff J, Gerstenberger PD, Munnings H, Tagle M, Sipe BW, Wehrmann T, Di Palma JA, Occhipinti KE, Barbi E, Riphaus A, Amann ST, Tohda G, McClellan T, Thueson C, Morse J, Meah N. Endoscopist-directed administration of propofol: a worldwide safety experience. *Gastroenterology* 2009; **137**: 1229-137; quiz 1229-137; [PMID: 19549528 DOI: 10.1053/j.gastro.2009.06.042]

45 **Dumonceau JM**, Riphaus A, Beilenhoff U, Vilmann P, Hornslet P, Aparicio JR, Dinis-Ribeiro M, Giostra E, Ortmann M, Knape JT, Ladas S, Paspatis G, Ponsioen CY, Racz I, Wehrmann T, Walder B. 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 [PMID: 23702777 DOI: 10.1055/s-0033-1344142]

46 **Triantafillidis JK**, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. *World J Gastroenterol* 2013; **19**: 463-481 [PMID: 23382625 DOI: 10.3748/wjg.v19.i4.463]

47 **Chandrasekhara V**, Early DS, Acosta RD, Chathadi KV, Decker GA, Evans JA, Fanelli RD, Fisher DA, Foley KQ, Fonkalsrud L, Hwang JH, Jue T, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Sharaf R, Shergill AK, Cash BD. Modifications in endoscopic practice for the elderly. *Gastrointest Endosc* 2013; **78**: 1-7 [PMID: 23664042 DOI: 10.1016/j.gie.2013.04.161]

48 **Wani S**, Azar R, Hovis CE, Hovis RM, Cote GA, Hall M, Waldbaum L, Kushnir V, Early D, Mullady DK, Murad F, Edmundowicz SA, Jonnalagadda SS. Obesity as a risk factor for sedation-related complications during propofol-mediated sedation for advanced endoscopic procedures. *Gastrointest Endosc* 2011; **74**: 1238-1247 [PMID: 22136773 DOI: 10.1016/j.gie.2011.09.006]

49 **Riphaus A**, Lechowicz I, Frenz MB, Wehrmann T. Propofol sedation for upper gastrointestinal endoscopy in patients with liver cirrhosis as an alternative to midazolam to avoid acute deterioration of minimal encephalopathy: a randomized, controlled study. *Scand J Gastroenterol* 2009; **44**: 1244-1251 [PMID: 19811337 DOI: 10.1080/00365520903194591]

50 **Correia LM**, Bonilha DQ, Gomes GF, Brito JR, Nakao FS, Lenz L, Rohr MR, Ferrari AP, Libera ED. Sedation during upper GI endoscopy in cirrhotic outpatients: a randomized, controlled trial comparing propofol and fentanyl with midazolam and fentanyl. *Gastrointest Endosc* 2011; **73**: 45-51, 51.e1 [PMID: 21184869 DOI: 10.1016/j.gie.2010.09.025]

51 **Suh SJ**, Yim HJ, Yoon EL, Lee BJ, Hyun JJ, Jung SW, Koo JS, Kim JH, Kim KJ, Choung RS, Seo YS, Yeon JE, Um SH, Byun KS, Lee SW, Choi JH, Ryu HS. Is propofol safe when administered to cirrhotic patients during sedative endoscopy? *Korean J Intern Med* 2014; **29**: 57-65 [PMID: 24574834 DOI: 10.3904/kjim.2014.29.1.57]

52 **Shergill AK**, Ben-Menachem T, Chandrasekhara V, Chathadi K, Decker GA, Evans JA, Early DS, Fanelli RD, Fisher DA, Foley KQ, Fukami N, Hwang JH, Jain R, Jue TL, Khan KM, Lightdale J, Pasha SF, Sharaf RN, Dominitz JA, Cash BD. Guidelines for endoscopy in pregnant and lactating women. *Gastrointest Endosc* 2012; **76**: 18-24 [PMID: 22579258 DOI: 10.1016/j.gie.2012.02.029]

53 **Ferreira AO**, Riphaus A. Patient-controlled sedation in endoscopy: are patients leading us? *Endoscopy* 2013; **45**: 920-921 [PMID: 24165818 DOI: 10.1055/s-0033-1344953]

54 **Poincloux L**, Laquière A, Bazin JE, Monzy F, Artigues F, Bonny C, Abergel A, Dapoigny M, Bommelaer G. A randomized controlled trial of endoscopist vs. anaesthetist-administered sedation for colonoscopy. *Dig Liver Dis* 2011; **43**: 553-558 [PMID: 21450542 DOI: 10.1016/j.dld.2011.02.007]

55 **Sieg A**, Beck S, Scholl SG, Heil FJ, Gotthardt DN, Stremmel W, Rex DK, Friedrich K. Safety analysis of endoscopist-directed propofol sedation: a prospective, national multicenter study of 24 441 patients in German outpatient practices. *J Gastroenterol Hepatol* 2014; **29**: 517-523 [PMID: 24716213]

56 **Simón MA**, Bordas JM, Campo R, González-Huix F, Igea F, Monés J. [Consensus document of the Spanish Association of Gastroenterology on sedoanalgesia in digestive endoscopy]. *Gastroenterol Hepatol* 2006; **29**: 131-149 [PMID: 16507280]

57 **Igea F**, Casellas JA, González-Huix F, Gómez-Oliva C, Baudet JS, Cacho G, Simon MÁ, de la Morena E, Lucendo A, Vida F, López-Rosés L. Sedation for gastrointestinal endoscopy. Clinical practice guidelines of the Sociedad Española de Endoscopia Digestiva. *Rev Esp Enferm Dig* 2014; **106**: 195-211 [PMID: 25007017]

58 **Dumonceau JM**, Riphaus A, Aparicio JR, Beilenhoff U, Knape JT, Ortmann M, Paspatis G, Ponsioen CY, Racz I, Schreiber F, Vilmann P, Wehrmann T, Wientjes C, Walder B. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Guideline: Non-anaesthesiologist administration of propofol for GI endoscopy. *Eur J Anaesthesiol* 2010; **27**: 1016-1030 [PMID: 21068575 DOI: 10.1097/EJA.0b013e32834136bf]

59 **Perel A**. Non-anaesthesiologists 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 [PMID: 21705907 DOI: 10.1097/EJA.0b013e328348a977]

60 **Pelosi P**. 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-anaesthesiologist administration of propofol for gastrointestinal endoscopy. *Eur J Anaesthesiol* 2012; **29**: 208; author reply 208-209 [PMID: 22273832 DOI: 10.1097/EJA.0b013e32834f5e5a]

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**Table 1 Pharmacologic profile of commonly used drugs for procedural sedation**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drugs** | **Onset of action (min)** | **Duration of action (min)** | **Usual doses** | **FDA pregnancy category** | **Adverse effects** |
| Pethidine | 3-6 | 60-180 | 25-100 mg | C | Respiratory depression, vomiting |
| Fentanyl | 1-2 | 30-60 | 50-200 μg | C | Respiratory depression, vomiting |
| Alfentanyl | < 1 | 30-60 | 0.250-2 mg | C | Respiratory and cardiovascular depression |
| Midazolam | 1-2 | 15-80 | 1-6 mg | D | Respiratory depression, disinhibition |
| Propofol | < 1 | 4-8 | 40-400 mg | B | Respiratory and cardiovascular depression |
| Flumazenil | 1-2 | 60 | 0.1-1 mg | C | Agitation, withdrawal symptoms |
| Naloxone | 1-2 | 30-45 | 0.2-1 mg | B | Narcotic withdrawal |

**Table 2 Meta-analysis of randomized controlled trials of propofol versus traditional sedation in endoscopy**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Procedures** | **Sedation compared**  | **No. of studies (cases)** | **OR (95%CI) for adverse events** |
| Qadeer *et al*[23], 2005 | EGD/colonoscopy/ERCP/EUS | Propofol *vs* traditional sedation | 12 (1161) | 0.74 (0.44-1.24) |
| Singh *et al*[2], 2008 | Colonoscopy | Propofol *vs* traditional sedation | 22  | Hypoxia: 0.69 (0.25-1.89); Hypotension: 1.03 (0.28-3.83)  |
| Bo *et al*[21], 2011 | ERCP | Propofol *vs* traditional sedation | 6 (663) | 1.69 (0.82-3.50) |
| Garewal *et al*[24], 2012 | ERCP | Propofol *vs* traditional sedation | 4 (510) | narrative |
| Wang *et al*[1], 2013 | EGD/colonoscopy/ERCP | Propofol *vs* traditional sedation | 22 (1798) | 0.90 (0.70-1.17) |

EGD: Esophagogastroduodenoscopy.

**Table 3 Existing societal guidelines for non-anesthesiologist administration of propofol**

|  |  |  |
| --- | --- | --- |
| **Scientific society** | **Limitations** | **Consider anethesiologist** |
| Sociedad Española de Endoscopia Digestiva (SEED), 2014 | Complex procedure; ASA III | ASA ≥ III; long/complex procedure; difficult airway |
| Austrian Society of Gastroenterology and Hepatology (OGGH), 2007 | n/a | n/a |
| Canadian Association of Gastroenterology (CAG), 2008 | n/a | ASA ≥ III; long/complex procedure; difficult airway |
| German S3 guidelines - DGVS/DGAI, 2008 | ASA ≥ III; long/complex procedure; difficult airway | ASA ≥ IV; long/complex procedure; difficult airway |
| European Society of Gastrointestinal Endoscopy (ESGE/ESGENA), 2010/2013 | n/a | ASA ≥ III; long/complex procedure; difficult airway |
| American multisociety guideline - AGA/ACG/ASGE/AASLD, 2009/2012 | n/a | ASA ≥ III; long/complex procedure; difficult airway |

ASGE: American Society of Gastrointestinal Endoscopy.