

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

Alexandre Oliveira Ferreira, Marília Cravo

Alexandre Oliveira Ferreira, Serviço de Gastreenterologia, Centro Hospitalar do Algarve, Unidade Hospitalar de Portimão, 8500 Portimão, Portugal

Marília Cravo, Serviço de Gastreenterologia, Hospital Beatriz Ângelo, 2674-514 Loures, Portugal

Author contributions: Ferreira AO and Cravo M contributed equally to this manuscript.

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Correspondence to: Alexandre Oliveira Ferreira, MD, Serviço de Gastreenterologia, Centro Hospitalar do Algarve, Unidade Hospitalar de Portimão, Sítio do Poço Seco, 8500 Portimão, Portugal. [alex.gastrohep@gmail.com](mailto:alex.gastrohep@gmail.com)

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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 ma-

intaining 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.

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

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**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<sup>[1,2]</sup> and procedural quality<sup>[3]</sup>. 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 alfentanil), 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  $\gamma$ -aminobutyric acid (GABA) receptor and enhancing its' inhibitory actions on the central nervous system. Midazolam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and antegrade amnesic properties<sup>[4]</sup>. 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<sup>[5,6]</sup>. 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<sup>[7]</sup> but frequently a state of deep sedation is inadvertently achieved, at least when used in combination with an opioid<sup>[8]</sup>.

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<sup>[9]</sup>.

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 dura-

tion 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<sup>[10]</sup>.

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)<sup>[11]</sup>. 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<sup>[7]</sup>. Transient pain on injection site is common, affecting up to 50% of patients<sup>[12]</sup>. 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<sup>[13]</sup>.

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 fiberoptic 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<sup>[14]</sup>, variable stiffness colonoscopes<sup>[15]</sup>, CO<sub>2</sub> insufflation<sup>[16]</sup> and water immersion techniques (in colonoscopy)<sup>[17]</sup> 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<sup>[18]</sup>. 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<sup>[19]</sup>. This set the *rationale*

**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
Alfentanil	< 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

for the so called traditional sedation.

After almost two decades there was the advent of midazolam<sup>[6]</sup>. 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<sup>[20]</sup>. 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<sup>[12]</sup> 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 anesthesiologists 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<sup>[11]</sup>. 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<sup>[1,2,21-23]</sup>. These improvements are achieved without an increased risk for adverse events as shown in several meta-analyses of randomized controlled trials (RCT)<sup>[1,2,24]</sup>. 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<sup>[25,26]</sup>. It may, however, be associated with a slightly higher risk for aspiration pneumonia<sup>[26]</sup>. 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<sup>[27]</sup>. 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<sup>[28-32]</sup>, it is still underused in most settings, because of medico-legal aspects, namely the requirement of an anesthesiologist and, consequently, increased costs<sup>[33]</sup>.

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<sup>[34]</sup>.

There is wide variability in sedation practice worldwide. In the United States the number of endoscopic procedures is increasing<sup>[35]</sup>, 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<sup>[36]</sup> and it's expected to pass the 50% mark by 2015<sup>[37]</sup>. On the other hand, non-anesthesiologist administration of propofol (NAAP) is becoming less common, as a result of Medicare reimbursement change in 2009<sup>[38]</sup>, 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<sup>[39]</sup> with colonoscopies being more likely to receive some form of sedation<sup>[33]</sup>. The countries with highest rates of propofol sedation are probably Switzerland<sup>[40]</sup> and Germany<sup>[41]</sup> 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<sup>[32,42-45]</sup>.

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<sup>[46]</sup>, 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<sup>[47]</sup>.

Obesity is a growing pandemic, especially in the United States. Obesity is frequently associated with other comorbidities and is considered an independent risk factor hypoxemia and the need for airway permeabilization maneuvers<sup>[48]</sup>. 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<sup>[46]</sup>.

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. Riphaut *et al.*<sup>[49]</sup> performed a RCT that showed that propofol sedation was superior to midazolam in terms of recovery times and cognitive impairment after EGD<sup>[49]</sup>. A larger RCT comprising 211 patients confirmed these findings<sup>[50]</sup>. In a more recent RCT, in South Korea, propofol was shown to be safe in cirrhotic patients comparing to healthy controls<sup>[51]</sup>. 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 be made because of the

possible risks to the fetus and are discussed in a ASGE guideline<sup>[52]</sup>. 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  $\geq$  III patients, since most evidence on NAAP is on low risk patients and death have been reported only in ASA  $\geq$  III patients<sup>[44]</sup>.

## 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)<sup>[1,2,21,23,24]</sup>. 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<sup>[53]</sup>.

To address this issue there is only one RCT<sup>[54]</sup>. This study by Poincloux *et al.*<sup>[54]</sup> 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 (94 mg 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 to 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.*<sup>[38]</sup> published in 2009 a sum of all published evidence on NAAP and collected unpublished prospective and retrospective records from several centers all



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

Ref.	Procedures	Sedation compared	No. of studies (cases)	OR (95%CI) for adverse events
Qadeer <i>et al</i> <sup>[23]</sup> , 2005	EGD/colonoscopy/ERCP/EUS	Propofol vs traditional sedation	12 (1161)	0.74 (0.44-1.24)
Singh <i>et al</i> <sup>[2]</sup> , 2008	Colonoscopy	Propofol vs traditional sedation	22	Hypoxia: 0.69 (0.25-1.89); Hypotension: 1.03 (0.28-3.83)
Bo <i>et al</i> <sup>[21]</sup> , 2011	ERCP	Propofol vs traditional sedation	6 (663)	1.69 (0.82-3.50)
Garewal <i>et al</i> <sup>[24]</sup> , 2012	ERCP	Propofol vs traditional sedation	4 (510)	Narrative
Wang <i>et al</i> <sup>[1]</sup> , 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 anesthesiologist
Sociedad Española de Endoscopia Digestiva, 2014	Complex procedure; ASA III	ASA ≥ III; long/complex procedure; difficult airway
Austrian Society of Gastroenterology and Hepatology (OGGH), 2007	NA	NA
Canadian Association of Gastroenterology, 2008	NA	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	NA	ASA ≥ III; long/complex procedure; difficult airway
American multisociety guideline - AGA/ACG/ASGE/AASLD, 2009/2012	NA	ASA ≥ III; long/complex procedure; difficult airway

ASGE: American Society of Gastrointestinal Endoscopy; NA: Not available.

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<sup>[13]</sup>. Recently, a large German experience of 24 441 cases on propofol and propofol with midazolam has been published<sup>[55]</sup>. 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*<sup>[34]</sup>, 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<sup>[28-32,45,56,57]</sup>. 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<sup>[29]</sup> and the European Journal of Anesthesiology<sup>[58]</sup>. 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<sup>[59]</sup> 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<sup>[60]</sup>.

## 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.

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