Anesthesia Outside the Operating Room (2 ed.)

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Anesthesia for Gastrointestinal Endoscopic Procedures

Chapter: Anesthesia for Gastrointestinal Endoscopic Procedures

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Introduction

For years, the number of endoscopic procedures performed by gastroenterologists in the United States has grown, and this trend continues. The escalating demand for endoscopic services can be attributed to an aging patient population, increased public awareness of cancer-screening benefits, and Medicare reimbursement for surveillance colonoscopies.[1] In addition, the complexity and invasiveness of procedures that can be accomplished via endoscopy has increased, with these procedures often requiring a more complex anesthestic than the conscious sedation commonly associated with the endoscopy suite. This may include general anesthesia with endotracheal intubation. Confounding this surge in complex procedures, there has also been an increase in the severity and number of patient comorbidities as American Society of Anesthesiologists physical class 3 (ASA 3) and ASA 4 patients now account for a greater proportion of patients being cared for in the endoscopy suite. Just as the procedures and the patients have evolved, so

has the delivery of anesthesia. Not only has there been an increase in the use of general anesthetics, but also there has been continued investigation of both non–anesthesiologist-administered propofol (NAAP) as well as patient-administered sedation and target-controlled infusions (TCIs) as an attempt to balance the increased need for sedation services with the shortage of available anesthesiologists.[2]

Sedation for endoscopy facilitates the procedure, improves patient tolerance and satisfaction, and increases the likelihood that the patient will agree to further interventions.[3] Historically, sedation regimens for endoscopy have consisted of a benzodiazepine combined with an opioid administered by nursing personnel under direction of the endoscopist. In the United States, the most common combination is midazolam with fentanyl.[1] For screening colonoscopies in low-risk patients, this model usually proves successful. However, many modern endoscopic procedures are prolonged and complex, necessitating the need for deep sedation or general anesthesia. Along with an increasing volume of pediatric patients, these factors are altering sedation practices in the endoscopy suite. Although options for non–anesthesiologist-administered sedation are common for many endoscopic procedures, in situations such as these, the use of an anesthesiologist is increasing.

The administration of anesthesia or sedation for endoscopy is associated with unique challenges that often differ from those encountered when providing anesthesia care in the operating room (OR). The location where procedures are performed (Figure **19.1**), inconsistencies in preoperative preparation, postanesthesia recovery issues, and the management of complications are all areas requiring distinctive management strategies in the non–operating room anesthesia (NORA) environment.

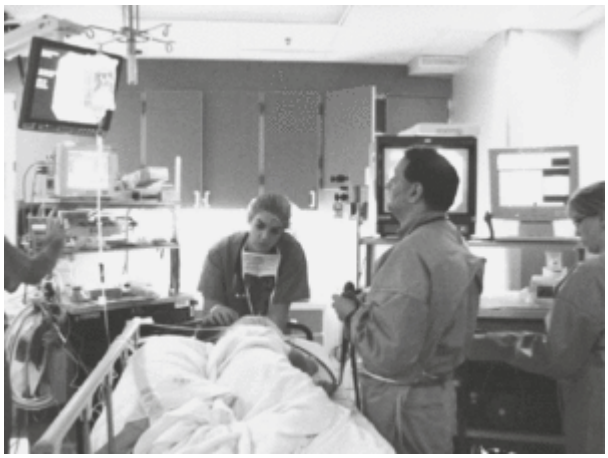

Figure 19.1.
Typical procedure room in gastrointestinal (GI) endoscopy suite.

Locations

A 2006 survey of randomly selected members of the American College of Gastroenterology attempted to determine the locations where endoscopy procedures are commonly performed in the United States as well as the types of sedation utilized for these procedures. The survey revealed that the majority (55.2%) of gastrointestinal (GI) endoscopies are still being performed in the hospital setting, although a significant number are being performed in ambulatory surgery centers.[1] Procedures performed in an office-based setting remain uncommon. Of note, there were significant regional differences in facility preference as well as sedation methods and percentage of cases in which an anesthesia professional administered the sedation.[1] While there have been several publications within the gastroenterology literature documenting and supporting the administration of propofol by nurses supervised by the gastroenterologist,[4,5,6] this practice does not yet seem to have achieved widespread acceptance. A variety of factors likely explain this, including the restriction in the product labeling of propofol (which is discussed further in the chapter) as well as state-specific nursing regulations. Several state nursing boards do not allow registered nurses to administer propofol for procedural sedation.

Sedation Versus General Anesthesia

Sedation for every procedure in the endoscopy suite is not ubiquitous; indeed, a small number of patients will tolerate simple GI endoscopic procedures without any sedation. While over 98% of colonoscopies and esophagogastroduodenoscopies (EGDs) are performed with sedation in the United States,[1] unsedated examinations are more common in other countries. European studies have sought to elucidate patient factors that might predict poor tolerance of endoscopy without sedation.[7] Apprehension about the procedure and elevated levels of anxiety were both associated with poor patient tolerance. Recent studies have also been performed to determine factors that influence increased sedation needs. These characteristics include female gender, younger age, difficult endoscopy, current use of opioids or benzodiazepines, and involvement of a trainee during the procedure.[8,9]

Healthy patients undergoing simple procedures such as screening colonoscopies or EGDs will generally tolerate these procedures well with light-to-moderate sedation. While some centers will utilize anesthesia care providers for these cases, a majority of gastroenterologists will direct nurse-administered sedation for these routine procedures. Most GI endoscopy centers will consult anesthesiologists for specific patient groups (Box 19.1), such as pediatric patients, patients with a history of being difficult to sedate, mentally challenged patients, and patients with life-threatening medical conditions. In these more challenging situations,

it is likely that deep sedation or general anesthesia will be required to achieve patient comfort and cooperation.

Box 19.1. Patients Likely to Require Sedation for Gastrointestinal Endoscopy

- Pediatric patients
- Patients with a history of being difficult to sedate or history of difficult intubation
- Substance abusers
- Mentally challenged patients
- Patients undergoing complex/long procedures
- Patients with serious or life-threatening medical conditions

To choose the appropriate level of sedation for an endoscopic procedure, the anesthesia provider must consider several variables. The patient's medical status is paramount in this decision, including whether the patient is at risk for aspiration, thus requiring endotracheal intubation. The logistics of the procedure also come into play when formulating an anesthetic plan, namely, the complexity and length of the planned procedure, positioning requirements, and proximity of the anesthesiologist to the patient's airway during the case.

Scheduling and the Preprocedure Evaluation

The same principles of preanesthetic evaluation for surgical cases should apply to GI endoscopic procedures.[10] This may require significant coordination between the anesthesia provider and the endoscopist, especially when dealing with medically complex patients. While many patients are evaluated by the gastroenterologist in an office visit prior to the procedure, the open-access model has become increasingly popular.[11] In this model, patients are referred by a primary care provider and scheduled for procedures without first being seen by the endoscopist. Most centers that employ an open-access scheduling system have a patient-screening process in place. For example, the endoscopy scheduler will conduct a telephone interview and review the patient's medical history. Affirmative answers to specific questions (i.e., history of heart failure, anticoagulant therapy) trigger a preprocedure office visit with the physician who will be performing the endoscopy.

It is critical that the gastroenterologist and anesthesiologist communicate, and the expectations regarding preanesthetic evaluations are understood. A well-defined process of evaluating each patient preendoscopy for anesthetic risks helps to avoid the frustrating scenario

in which the anesthesiologist is faced with an inadequately evaluated patient moments before the procedure is scheduled to begin.

An excellent example of a situation that requires preprocedure planning is that of managing antiplatelet medications and anticoagulants in preparation for endoscopic procedures where bleeding is expected, such as esophageal varices banding or endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy. As the indications for long-term anticoagulant/antiplatelet therapy expand, the number of patients presenting to the endoscopy suite who are taking these medications also is increasing. This issue is of particular importance in patients who have drug-eluting coronary stents. As with surgical patients, the decision whether to withhold these medications during the periprocedure period is complex and must be made in collaboration with the gastroenterologist, cardiologist, and anesthesiologist. An approach that has been studied and shown to be cost effective is to perform a primary diagnostic endoscopy while the patient remains on the usual anticoagulation regimen. An informed decision can then be made on how to manage the anticoagulants if a therapeutic procedure is deemed necessary.[12] It is somewhat reassuring that a retrospective case-control study concluded that antiplatelet agents were not significantly associated with bleeding after endoscopic sphincterotomy.[13] However, a recent survey indicated that as many as 26% of 239 US endoscopists felt that they would advise discontinuation of all antiplatelet agents before performing any endoscopic procedure, including low-risk procedures, despite the recommendations of previous American Society of Gastrointestinal Endoscopy (ASGE) guidelines.[14] This information further justifies the need for a multidisciplinary approach to decision-making about withholding these medications for each patient.

An important aspect of the preanesthetic evaluation is determining whether the endoscopy suite is the most appropriate location for performing the procedure. Unlike other nonsurgical procedures requiring anesthesia services, the equipment necessary to perform many GI procedures is relatively portable. From the anesthesiologist’s perspective, the OR may be the safest environment for performing endoscopy in the most medically challenging patients. Specialized monitoring and airway equipment as well as additional anesthesiology personnel are more readily available if anesthesia complications arise.

Reimbursement

Payers do not typically provide separate reimbursement for sedation when a gastroenterologist both performs the procedure and oversees the sedation; the sedation component is included. As an increasing number of endoscopists have turned to anesthesiologists to provide sedation, charges to Medicare for anesthesia for colonoscopy have increased markedly. Between 2001 and 2003, the number of colonoscopies in which anesthesiologists provided sedation more than doubled, and charges to Medicare increased 86%.[15] This rapid growth

attracted increased scrutiny from commercial payers and Medicare contractors. Many carriers distinguish between anesthesia for low-risk and high-risk patients, allowing reimbursement for the latter only. Carriers set guidelines to define a high-risk patient or procedure, and case-specific reasons that necessitate the participation of an anesthesia care provider must be documented accordingly.

In addition, significant regional differences exist that highlight disparities in reimbursement policies across the country, and this explains why anesthesia for endoscopy tends to be handled differently depending on the location. For instance, a 2004 survey showed that in the northeastern states, where carriers are generally unfavorable toward anesthesiologist involvement, only 7% of gastroenterologists used propofol sedation. In the mid-Atlantic states where more favorable policies exist, 43% of gastroenterologists utilized anesthesiologists to administer propofol.[1]

Despite these regional variations, 2016 brought with it a significant decrease in colonoscopy reimbursement across all regions, which has further complicated the participation of anesthesia providers. Prior to the reduction in reimbursement, studies had indicated that the actual procedure times were significantly less than the times on which the relative values for endoscopy had been based. This led the Centers for Medicare and Medicaid Services (CMS) to enact lower reimbursement for GI endoscopy beginning in 2016. They upheld their standard that colonoscopy coding still includes moderate sedation, thus preventing an endoscopist from adding additional coding for supervision of moderate sedation. However, they did stipulate that a second physician, other than the one performing the procedure, may report the codes for moderate sedation or anesthesia if he or she provides this service, thus acknowledging the importance of a dedicated anesthesia provider in some circumstances.[16]

Finally, in the interest of making preventive care more widely available, a provision of the Affordable Care Act waived “colorectal cancer screening test” copayments and deductibles for Medicare and other beneficiaries. Included in this ruling on physician fee schedules is the inclusion of anesthesia services furnished in conjunction with a screening colonoscopy, thus preventing a separate bill to the patient for a copay or deductible.[17] By including anesthesia services within the necessity of preventive medicine, the CMS further validated the role of the anesthesia provider even for screening procedures.

Medications for Sedation and Analgesia

The sedation regimen for the majority of GI endoscopic procedures consists of a benzodiazepine combined with an opioid titrated to mild-to-moderate sedation.[18] As procedure numbers climb and techniques become more sophisticated, some limitations of this traditional sedation practice are discovered. There are patients who simply cannot be adequately sedated with a benzodiazepine/opioid

combination, leading to failed procedural attempts or a poor experience for the patient. Onset of sedation can be prolonged with these two classes of drugs, and significant side effects are not uncommon in the recovery period, including nausea, vomiting, prolonged sedation, and respiratory depression. For these reasons, alternative drugs have been sought that offer improved pharmacodynamic profiles coupled with fewer side effects.[19]

Propofol

While the issue of propofol administration by nonanesthesia personnel is controversial, there is little doubt that propofol is perhaps the most desired agent for endoscopic sedation.[20] High patient satisfaction, quick onset, rapid recovery, and improved operational efficiency are all factors that have led to increased demand for propofol use in the endoscopy suite. Depending on the type and duration of procedure, it can be administered as either intermittent boluses or a continuous infusion. One of the drug's disadvantages, though, is its very narrow therapeutic window. Due to significant variation among patients, it is not uncommon for a dose that typically produces moderate sedation to lead to a level of deep sedation or even general anesthesia in some patients. Unlike use of opioids and benzodiazapines, propofol currently does not have a reversal agent in case of oversedation. As a result, the US Food and Drug Administration (FDA) includes on propofol's product label a statement that it "should only be administered by persons trained in the administration of general anesthesia."[21] In addition, the American Society of Anesthesiologists "Practice Guidelines for Sedation and Analgesia by Non-anesthesiologists"[22] and The Joint Commission state that practitioners providing sedation should be able to manage patients who reach a deeper level of sedation than was planned. In the case of propofol administration, therefore, the practitioner should be competent in managing airway obstruction and respiratory depression, which could include the need for endotracheal intubation, as well as cardiovascular side effects such as hypotension. It is these positions by regulatory and accrediting agencies, which are supported by the American Society of Anesthesiologists, that have made the administration of propofol by nonanesthesia professionals, including registered nurses under the supervision of an endoscopist, a controversial topic.

In an article published in 2009, the argument for endoscopist-directed propofol (EDP) administration was made citing over 646,000 patients who received propofol for either upper endoscopy or colonoscopy in which there were just 4 deaths and 11 endotracheal intubations. Not all studies that were included in this analysis included data on the use of positive pressure ventilation, airway assist devices such as oral airways, or periods of apnea.[23] This retrospective study is limited based on reliance of self-reporting by each institution, including reporting based on memory rather than formal records and no uniform method of sedation with both single-agent propofol and balanced anesthesia with inclusion of opioids

and benzodiazepines along with propofol, used by facilities providing data for the analysis.

The incidence of complications such as oxygen desaturation and airway obstruction associated with Nurse Administered Propofol Sedation (NAPS) is not well defined. Some gastroenterologists are now reporting the use of NAPS for more complex endoscopic procedures, such as endoscopic ultrasound (EUS).[24,25] In a retrospective study of more than 800 patients, 0.5% of patients required positive pressure ventilation during the procedure, and oxygen saturation decreased below 90% in 0.7% of patients.[24] This led one proponent of NAPS for simple endoscopic procedures to caution about adopting this technique for more advanced procedures.[26]

A meta-analysis that looked at the pooled results of sedation comparing NAPS with an anesthesia provider (anesthesiologist or certified registered nurse anesthetist [CRNA]) sedation for complex procedures including ERCP, EUS, and small intestine deep enteroscopy had interesting results. The NAPS sedations tended to use less propofol and require less airway intervention; however, patient and endoscopist satisfaction were significantly higher in the anesthesia professional group. Both groups had similar rates of desaturation.[27]

In 2015, the European Society of GI Endoscopy and the European Society of Gastroenterology and Endoscopy Nurses issued updated guidelines with recommendations limiting the scope of NAPS based on the patient's physical status, airway classification, body mass index (BMI), and anticipated long or complex procedures. Also included in these guidelines was the recommendation that propofol be used only as a single agent rather than as part of a balanced anesthetic. They further recommended use of propofol as patient-controlled sedation (PCS) or a TCI.[28]

Patient-controlled sedation is a delivery model that has been investigated for use in endoscopic procedures as a way to provide adequate sedation while minimizing the problem of oversedation that can occur due to propofol's narrow therapeutic window.[29,30] Although PCS with propofol and other medications has been investigated for endoscopy and has been shown to be safe and effective, PCS has not gained widespread acceptance for these procedures within the United States. Multiple studies have shown that when comparing PCS to both anesthesia provider- and nurse-administered sedation, medication doses tended to be lower, sedation levels lighter, and recovery times faster for PCS.[31,32,33,34,35,36,37] However, varying results have been found with PCS in regard to patient and endoscopist satisfaction.[33,35,37]

A prospective randomized study from France compared PCS with propofol administration by an anesthesiologist for patients undergoing colonoscopy. Patients in the patient-controlled group self-administered 20-mg boluses of propofol as needed with a 1-minute lockout time. Patients in the anesthesiologist-controlled group received a continuous infusion of

propofol that was titrated to effect. Procedural success, which was defined as reaching the cecum with the colonoscope, and technical ease of the procedure as rated by the gastroenterologist did not differ between the groups. Patient satisfaction was similar between the groups as well. Patients in the patient-controlled propofol group experienced a lighter depth of sedation and used significantly less propofol than patients in the anesthesiologist-controlled group. In addition, fewer episodes of desaturation occurred in the patient-controlled group, and the time to discharge was also shorter in this group.[38]

Target controlled infusion systems also continue to be investigated and are used in about 90 countries; however, they are not FDA approved in the United States. A TCI of propofol uses a pharmacokinetic model to achieve and maintain a selected target blood propofol concentration, thereby avoiding the peaks and troughs associated with bolus dosing. A 2014 study comparing patients undergoing colonoscopy and EGD procedures with fentanyl/midazolam sedation versus NAPS with a TCI of propofol found that both patient and endoscopist satisfaction were significantly higher for the TCI group.[39] Research has been done comparing a manually controlled infusion of propofol with a TCI infusion, with both administered by nonanesthesia personnel. Although the TCI infusion offered some promising results, there were adverse events in both groups (including prolonged hypoxemia) that required advanced airway management.[40]

In 2013, the FDA approved the propofol-based sedation product SEDASYS, a computer-assisted personalized anesthesia system.[41] By integrating real-time patient data into a computer program, the system managed the delivery of propofol for both colonoscopies and EGD procedures. The ASA had recommended that the system be limited to patients over the age of 18 and only in locations where anesthesia professionals were immediately available. Concerns with the system included its use in patients who could develop airway complications, such as the morbidly obese population, patients with obstructive sleep apnea, and patients with respiratory complications. However, by March 2016 Johnson and Johnson had discontinued the device due to poor sales.[42]

While it may not be clear which practitioners and delivery methods will be used most commonly in the future, it is certain that propofol will continue to be a popular drug administered for sedation and anesthesia during endoscopic procedures.

Dexmedetomidine

Approved by the FDA in 1999 for sedation for intubated patients in the intensive care unit, dexmedetomidine is a highly selective α_2-adrenergic receptor agonist with sedative and analgesic effects.[43] Agonism at presynaptic receptors in peripheral sympathetic nerves inhibits the release of norepinephrine, while stimulation at central postsynaptic receptors serves to inhibit sympathetic activity. As the drug’s mechanism

of action is unrelated to the γ-aminobutyric acid (GABA) system, the quality of sedation is purportedly different.[44] Patients tend to appear quite sedated yet are more easily arousable than patients sedated by a GABA-potentiating agent such as midazolam or propofol. A relatively new agent in the anesthesiologist's armamentarium, dexmedetomidine's role in sedation for GI endoscopy has not been entirely established.

Few studies have been performed evaluating the use of dexmedetomidine specifically for endoscopic procedures. A Turkish study published in 2007 compared dexmedetomidine and midazolam in a cohort of 60 ASA 1 and 2 adult patients undergoing EGD.[45] Endoscopist satisfaction with sedation quality was higher and total side effects were lower in the dexmedetomidine group. Recovery time and hemodynamic parameters were comparable between the two groups. A 2014 study evaluated upper endoscopy with midazolam sedation versus dexmedetomidine sedation. This small study (n = 60) concluded that patients sedated with dexmedetomidine had higher oxygen saturations and improved satisfaction as compared to the group sedated with midazolam.[46]

A study from Poland evaluating dexmedetomidine for sedation during colonoscopy found it to be less than ideal, and indeed, the study was terminated due to adverse events in the dexmedetomidine group.[47] Compared with patients receiving meperidine and midazolam or fentanyl as a single agent, patients receiving dexmedetomidine had the longest recovery time as well as significant bradycardia and hypotension not seen in the other groups. When evaluating dexmedetomidine sedation with propofol sedation, researchers found minimal differences in oxygen saturation and respiratory rate variability, yet patients in the propofol group had lower mean arterial pressures (MAPs), while those in the dexmedetomidine group experienced more bradycardia. Patients reported greater satisfaction with dexmedetomidine, and endoscopist satisfaction was comparable between the dexmedetomidine and propofol groups.[48]

Ketamine

A synthetic phencyclidine derivative, ketamine is a rapidly acting anesthetic agent that produces rapid sedation, amnesia, and analgesia.[49] Functioning as an *N*-methyl-D-aspartate (NMDA) receptor antagonist, ketamine acts to dissociate the limbic and cortical systems, producing a cataleptic state that does not resemble normal sleep patterns.[50]

Airway reflexes are generally maintained, and cardiovascular and respiratory side effects are minimal.

Ketamine has been examined both as a sole agent for sedation and in combination with other sedatives in both adults and children. Most literature references address its use in the pediatric population. Gigler et al. performed a retrospective analysis of 402 pediatric patients receiving various combinations of midazolam, meperidine, and ketamine for simple endoscopy procedures.[51] They concluded that the group that received

midazolam and ketamine in combination had the lowest rate of complications as well as an equal rate of adequate sedation when compared with other sedation regimens. A study from Hong Kong sought to evaluate the effectiveness of intramuscular ketamine as a sole sedative agent in 60 children undergoing basic GI endoscopic procedures as well as bronchoscopy.[52] It was determined that a single intramuscular dose of ketamine (2–3 mg/kg) was safe and effective for children aged 7 years and older. A high failure rate was noted in children younger than 7 years, with the highest failure rates among infants. Kirberg et al. described their successful use of ketamine, primarily as an adjunct to other sedatives, in over 900 pediatric endoscopic procedures.[53] Ketamine use in difficult-to-sedate adult patients undergoing ERCP and EUS has been explored.[54] In patients who were inadequately sedated with meperidine and diazepam, it was found that ketamine administration offered a better depth of sedation and shorter recovery time than additional dosing of meperidine and diazepam.

Benzodiazepines

Long an integral part of sedation for endoscopy, early benzodiazepines, such as diazepam, were not water soluble, leading to problems with administration. Once water-soluble midazolam became available in the late 1980s, it quickly gained favor.[55]

The majority of intravenous sedation for endoscopy today involves administration of midazolam in combination with an opioid, usually by a nonanesthesia professional.[1] Serious side effects from midazolam are uncommon, although dose-dependent respiratory depression does occur. This respiratory depression is more likely in patients who have underlying respiratory disease and in those receiving concomitant opioids for sedation.[18] A large prospective study of 2635 pediatric endoscopies at the Children’s Hospital of Philadelphia found only two serious adverse events (apnea) and concluded that administration of midazolam and fentanyl is safe for pediatric endoscopy.[56]

Opioids

The second component of the conventional sedation combination for endoscopy is an opioid. Twenty-five years ago, meperidine was the primary choice.[55] Today, meperidine has been supplanted by fentanyl as the predominant opioid used. Alternative opioids have been investigated for use in procedural sedation, such as the ultrashort-acting remifentanil. One study examined the use of remifentanil combined with a benzodiazepine in the sedation of 40 patients undergoing various procedures, including endoscopy.[57] While discharge times were short and analgesia was profound in the remifentanil group, the dose to achieve adequate sedation frequently led to apneic episodes requiring intervention. It was concluded that remifentanil use for sedation during brief procedures is not useful.

Remimazolam

Remimazolam is a benzodiazepine derivative now in phase 2 trials. Midazolam is the parent drug of remimazolam, which has been modified to include the pharmacokinetics of remifentanil.[58] GABA is the primary inhibitory neurotransmitter in the central nervous system, and like other anesthetics, remimazolam acts at GABA receptors (GABA-α) to elicit its sedative effects. Because the drug undergoes ester hydrolysis, which is dose independent, accumulation of the drug is not seen in clinical doses. In the phase 2 trials performed thus far, the time to recovery from sedation was shorter and more consistent with remimazolam when compared to midazolam. However, respiratory depressant effects have been reported in numerous studies.[59,60]

Sedation/Anesthesia for Specific Procedures

Gastrointestinal endoscopy procedures vary significantly in their complexity, duration, and degree of patient stimulation. Therefore, the anesthesiologist must tailor the sedation regimen to focus on not only individual patient requirements but also the unique variables associated with the procedure being performed.

Esophagogastroduodenoscopy

While many EGDs are performed successfully with a combination of a benzodiazepine and opioid, the majority of EGD sedations performed by anesthesiologists utilize propofol. A nationwide survey of gastroenterologists reported higher satisfaction rates with propofol compared to conventional benzodiazepine/opioid sedation.[1] The median satisfaction score for propofol was 10 on a scale where 10 was defined as best, while benzodiazepine and opioid in combination yielded a score of 8. Also, a majority of these physicians selected propofol as the agent they would choose to receive for their own endoscopy. Reasons given for favoring propofol included better sedation and analgesia, fast return to normal activity, and improved quality of the endoscopic examination.

While successful EGD exams can generally be performed under moderate sedation in most patients, individuals with a history of being difficult to sedate or a history of substance abuse will generally require deep sedation or general anesthesia. However, even when moderate sedation is the intended endpoint, studies have shown that deep sedation is often achieved. In one study, 60% of patients undergoing EGD reached a level of deep sedation despite a preprocedure plan for moderate sedation.[61]

A patient’s need for endotracheal intubation is another factor to consider when choosing between sedation and general anesthesia for EGD. Many of the indications for EGD, such as persistent vomiting or severe gastroesophageal reflux disease, may dictate protection of the airway with an endotracheal tube. Other patients who may not tolerate the level of sedation needed for EGD include patients with obstructive sleep apnea or morbid obesity. Significant airway obstruction should be expected in

these patients, and endotracheal intubation should be strongly considered.

One unique technique that has been employed for EGD under general anesthesia in pediatric patients is use of the ProSeal™ laryngeal mask airway (LMA).[62] The ProSeal LMA features a modified cuff and a drain tube that provides gastric access. The drain tube is of a sufficient size to accept pediatric-size gastroscopes. When compared with oxygen delivery via nasal cannula, the ProSeal group had overall higher SpO_2 values and fewer episodes of hypoxemia with no discernible difference between groups in ease of endoscopy.

An adjunct to sedation for EGD that is often overlooked is topical pharyngeal anesthesia. While there are studies that have reported no additional benefit from topical anesthesia in sedated patients,[63] other studies[64] as well as a meta-analysis[65] have reported an improvement in the ease of endoscopy in patients receiving topical pharyngeal anesthesia. It should be noted that commercially available local anesthetic sprays such as HurriCaine® and Cetacaine® sprays contain benzocaine, which has been associated with the development of methemoglobinemia.[66] Another novel method for topical anesthesia that has been described is use of a lidocaine lollipop.[67] In a study of 50 patients undergoing EGD, approximately one-third of those receiving the lidocaine lollipop did not require any further sedation throughout the procedure.

Colonoscopy

Like EGD, the majority of patients can be adequately sedated for colonoscopy with a combination of midazolam and opioid. One study found that when moderate sedation was planned, fewer patients progressed to deep sedation during colonoscopy than during EGD, ERCP, or EUS.[61] This might be explained by the less-stimulating nature of the colonoscopy exam when compared to the other procedures. However, most anesthesia providers who sedate patients for colonoscopy typically use propofol and aim for deep sedation or even general anesthesia. It seems likely that even in situations where the endoscopist is directing sedation, they and their patients prefer a deeper level of sedation. In a study of nurse-administered propofol sedation performed under the direction of a gastroenterologist, the mean bispectral index (BIS) score was found to be 59, indicating a state of general anesthesia.[68]

Several sedation techniques for colonoscopy have been studied. Moerman et al. compared intravenous remifentanil to intravenous propofol in 40 adult patients scheduled for complete colonoscopies. They found that measures of early recovery, such as spontaneous eye opening and following commands, occurred sooner in patients who received remifentanil than in patients who received propofol. In addition, recovery of cognitive function was quicker in the remifentanil group. However, patient satisfaction was lower in the remifentanil group, and respiratory depression was more common in this group as well.[69] Another study

evaluating the use of remifentanil for sedation during colonoscopy found postprocedure nausea and vomiting to be a significant problem.[70] General anesthesia using an inhalational technique of sevoflurane/nitrous oxide also has been compared with total intravenous anesthesia (TIVA) using propofol/fentanyl/midazolam for colonoscopy.[71] While emergence was quicker in the TIVA group, patients who received an inhalational anesthetic were less sedated 20 minutes after completion of the procedure. The TIVA group also experienced psychomotor impairment lasting 30–90 minutes longer than the inhalational group.

Propofol as a sole agent for sedation during colonoscopy has been compared to a combination of lower-dose propofol in combination with fentanyl or midazolam titrated to moderate sedation. Patients in the propofol-only group reached a deeper level of sedation than any of the combination groups. No differences in vital signs, adverse respiratory events, or patient satisfaction were found among the groups, although patients in the propofol-only group remembered less procedural pain. Patients who received a combination of propofol with midazolam or fentanyl were discharged more quickly, however.[72]

In a small study comparing propofol sedation versus midazolam and meperidine, the authors examined the cardiovascular effects between the two dosing regimens. The rates of hypotension, hypoxemia, and bradycardia were statistically insignificant between the two groups, yet the length of recovery for the propofol group was significantly longer.[73] Of note, this study looked primarily at ASA 1 and 2 patients. Only a small percentage of patients in each sedation group were ASA 3 patients, which might explain why there were no significant differences in cardiovascular effects between the sedation regimens. Further investigation including a patient population with significant comorbidities might find some subtle differences between sedation drugs that could not be identified when studying relatively healthy patients.

Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography combines endoscopy and fluoroscopy (Figure **19.2**) in a technique used to diagnose and treat diseases of the biliary and pancreatic ductal systems. Patients who present for ERCP are typically more severely ill than patients undergoing EGD or colonoscopy. Common presenting diagnoses include pancreatitis, bile duct or pancreatic cancer, sphincter of Oddi dysfunction, and cholangitis. The systemic illnesses in this patient population may partly account for the high risk of cardiopulmonary complications associated with ERCP. An Australian study that looked at ERCP complications related to patient age found that approximately 25% of patients 65 years or older developed new electrocardiographic changes (ischemia, arrhythmias) during or after ERCP. Elevated cardiac troponin I levels were documented in 11% of patients in this age group.[74] In comparison with colonoscopy or EGD, complex therapeutic procedures of significant duration are often undertaken during ERCP. Interventional techniques commonly employed

include placement of biliary stents, biliary sphincterotomy, removal of bile duct stones, and stricture dilation. Patient immobility is paramount for successful performance of these often time-consuming and challenging procedures. Adding to the challenge for the anesthesia provider is the prone position that most gastroenterologists prefer for performing ERCP.

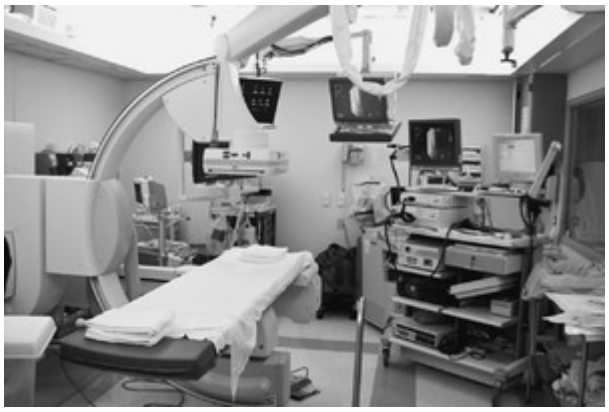

Figure 19.2.
Endoscopic retrograde cholangiopancreatography (ERCP) procedure room.

Given the multiple comorbidities that often accompany patients undergoing ERCP, it is not surprising that multiple studies have found higher incidences of cardiovascular and respiratory adverse events such as hypotension and hypoxemia during ERCP compared with other GI procedures, even when sedation is administered by anesthesiology personnel.[75,76] When comparing a sedation regimen of dexmedetomidine/ketamine versus propofol/fentanyl during ERCP, one study found fewer episodes of hypotension, desaturation, and bradycardia in the dexmedetomidine/ketamine group, yet this group also exhibited a significantly longer recovery time when compared to the propofol/fentanyl group.[77]

While many anesthesiologists prefer general anesthesia for ERCP, some do successfully provide moderate or deep sedation for this procedure. The preferred sedative drug is invariably propofol. Midazolam versus propofol sedation has been studied in the setting of ERCP.[78] Successful procedure completion was more likely in patients receiving propofol (97.5% vs. 80%), and recovery time was significantly shorter in the propofol group. TCI techniques have also been studied for use in ERCP sedation. Although cost effectiveness of the system requires further investigation, successful sedation for ERCP has been reported by titrating propofol to a target concentration of 2–5 μg/mL.[79] Mazanikov and colleagues from Helsinki, Finland, have done extensive research into PCS and have investigated numerous sedation methods for ERCP. In one study, they compared propofol delivery via TCI and PCS during ERCP. In the PCS group, propofol consumption was less, while patients were at

comparable levels of sedation in the recovery room when compared to TCI.[31] Mazanikov and colleagues also investigated PCS with propofol and remifentanil versus propofol and alfentanil. They concluded that PCS sedation with propofol and remifentanil was more likely to be associated with respiratory depression and postprocedural nausea than PCS sedation with propofol and alfentanil.[35]

The challenges associated with sedation for ERCP have led many anesthesiologists to prefer general anesthesia for the procedure. Data exist that support this clinical approach. A retrospective study of over 1000 ERCP procedures found the procedure failure rate with sedation to be double the failure rate with general anesthesia, usually due to inadequate sedation.[80] Complication rates may also be lower in patients receiving general anesthesia for therapeutic ERCP. The lower complication rate with general anesthesia is hypothesized to result from less patient movement and aperistalsis of the duodenum.[81]

Due to the prone position, inaccessibility of the airway to the anesthesiologist, and the presence of aspiration risk factors in many patients, endotracheal intubation is often performed when general anesthesia is chosen for ERCP. However, the use of the LMA for ERCP has been described by investigators, even in the prone position. In a group of 20 patients, no airway complications were encountered, and there were no technical difficulties with endoscope placement or ERCP performance.[82] In a study comparing TIVA without versus with endotracheal intubation in patients undergoing ERCP, they cited a 4.8% conversion rate to general endotracheal anesthesia. Reasons for having to place an endotracheal tube included retained food in the stomach or esophagus, patient movement, length of procedure, ventilation problems, and aspiration. In this study, the patients who were managed without intubation had shorter nonprocedural anesthesia times when compared to those who were intubated.[83]

Endoscopic Ultrasonography

Endoscopic ultrasonography is used for diagnosing and staging GI and pancreatic tumors and, like ERCP, is a more complex and stimulating procedure than EGD or colonoscopy. Frequently, needle aspiration biopsies are taken that must be examined by a pathologist before completion of the procedure. The long duration of the procedure coupled with the larger size of the ultrasound-containing endoscope results in an elevated level of patient discomfort when compared with simple EGD. As a result, adequate sedation for EUS typically requires deep sedation or general anesthesia.

Because achieving an appropriate level of sedation while avoiding hypoxemia and airway obstruction may be more challenging during EUS, many patients will not tolerate the procedure with the conventional benzodiazepine and opioid combination. Alternative strategies for sedation have been investigated. In one study, moderate doses of

benzodiazepine and opioid were given before the EUS procedure began. This baseline sedation was then supplemented during the procedure with either ketamine or additional benzodiazepine and opioid. The degree of patient comfort, technical ease of the study, and recovery times were all improved in the patients who received ketamine supplementation. In addition, approximately one-third of the patients randomized to receive additional benzodiazepine/opioid had to cross over to the ketamine group to obtain a sedation level adequate to complete the EUS.[54]

A propofol infusion controlled by an anesthesiologist is, of course, another popular option for EUS sedation. Other unique techniques have been explored, including propofol TCI and PCS. One group of investigators studied the effect of midazolam dosing on the amount of propofol required to successfully complete the EUS procedure. They found that preprocedure administration of midazolam did not significantly affect the dose of propofol used, but it also did not delay the time to discharge.[84] PCS using boluses of 3.75 µg fentanyl and 4.25 mg propofol without a lockout interval has also proved successful for sedation during EUS.[85] A retrospective cohort study found improved diagnostic yield during EUS with fine-needle aspiration of pancreatic masses when general anesthesia was provided for the procedure by an anesthesiologist compared to conscious sedation provided by a registered nurse.[86]

Natural Orifice Translumenal Endoscopic Surgery

Natural orifice translumenal endoscopic surgery (NOTES) is an emerging technique within the field of minimally invasive surgery. The aim of NOTES is to perform intra-abdominal procedures with peritoneal access via natural orifices in lieu of conventional abdominal incisions. Proposed advantages include fewer skin flora–based infections, elimination of incisional hernias, a reduction in postoperative pain, and a lower incidence of postoperative adhesions.[87]

Multiple experiments have been carried out in animal models evaluating the feasibility of NOTES for various operations, including cholecystectomy,[88] gastrojejunostomy,[89] tubal ligation,[90] and splenectomy.[91] The use of NOTES in humans is just beginning, although several groups have published case reports of successful transvaginal cholecystectomy.[92,93,94] Auyang et al. have described a transgastric approach to cholecystectomy in humans utilizing a hybrid of endoscopic and laparoscopic techniques.[95] The most common procedures by orifice that have been performed are transvaginal cholecystectomy, followed in descending order by transgastric peritoneoscopy, transgastric cholecystectomy, and transvaginal appendectomy. The majority of these procedures have been performed outside of the United States, accounting for 86% of the reported cases, versus just 14% performed within the United States.[96]

Most cases of NOTES in humans have been performed with the patient under general anesthesia, with a few exceptions.[97] Some have suggested a potential advantage of NOTES might be the ability to avoid general anesthesia because there is no skin incision.[98] While avoidance of an abdominal incision would certainly lessen analgesia requirements, most published descriptions of the technique have involved creation of a pneumoperitoneum in patients who are under general anesthesia. Peritoneal insufflation is generally poorly tolerated in the lightly sedated patient and can lead to cardiopulmonary embarrassment. While laparoscopic surgery has been performed under spinal anesthesia, its success hinges on specialized techniques to ensure patient comfort. Successful laparoscopic cholecystectomy under spinal anesthesia has been described in a small number of patients using nitrous oxide to create the pneumoperitoneum, utilizing low insufflation pressures, minimizing surgical traction, and inserting trochars below the umbilicus.[99] Whether spinal anesthesia is a useful technique for NOTES is a subject for future study.

In the future, with technological and surgical advancements, it is quite possible that natural orifice surgery will be performed in locations outside the OR. Like conventional endoscopy, the necessary equipment is portable and the approach is minimally invasive. If techniques are developed in which pneumoperitoneum can be avoided or its side effects minimized, it may be possible to perform NOTES under sedation or regional anesthesia. For now, it seems this unique blend of endoscopy and general surgery is best performed in the OR under general anesthesia.

Endoscopy for Pediatric Patients

The majority of pediatric patients will not tolerate GI endoscopy without deep sedation or general anesthesia. Anesthesiologists are therefore more likely to participate in pediatric procedures than adult procedures and, in some centers, are responsible for all or most pediatric sedations and anesthetics. While many of the techniques and drugs used are consistent across patient age groups, the pediatric population presents unique challenges. Typically, pediatric patients require larger doses of sedative medications on a per weight basis than adults. A group of investigators evaluating the median effective concentration of propofol required for EGD found that children aged 3–10 years required substantially higher plasma levels than adult patient groups undergoing the same procedure.[100]

One of the greatest challenges faced by the anesthesiologist in the endoscopy suite is obtaining intravenous access in children. In contrast with the OR where intravenous lines are generally started after inhalational induction of general anesthesia, it is often not practical to have an anesthesia machine available in this practice setting. Techniques to aid in placement of the intravenous line as well as separation from the parent are invaluable. In one study, preprocedural administration of oral midazolam (0.5 mg/kg) was found to improve the ease of intravenous line

placement, facilitate parental separation, improve patient comfort, and result in lower overall propofol use for upper endoscopy.[101] Recovery time was substantially longer in the children who had received midazolam, but it still averaged just 26 minutes.

The ideal sedation combination is still being investigated in children who undergo upper endoscopy without intubation. In a recent study that looked at upper endoscopy in children over the age of 4, it was found that a combination of ketamine and midazolam offered better tolerance of the procedure when compared to propofol and fentanyl. Neither group developed major complications, including aspiration, cardiac arrest, laryngospasm, or apnea; however, the ketamine/midazolam group did develop significantly more recovery side effects, including emergence reactions, delirium, dizziness, and nausea and vomiting. Those in this group also had a statistically significant longer recovery period when compared to the group sedated with propofol and fentanyl.[102]

Managing Complications

A large prospective cohort study has been performed examining the incidence of cardiopulmonary complications during propofol sedation for upper endoscopy and colonoscopy. Nearly 12,000 colonoscopies and 6000 EGDs in which patients received propofol sedation were examined. The overall rate of complications was 0.86% for colonoscopy and 1.01% for EGD. Serious adverse events, defined as death, perforation, or bleeding, occurred in just 18 patients receiving colonoscopy and 17 patients undergoing EGD. Of note, the complication rate was lower for both procedures when sedation was provided by anesthesia providers rather than the gastroenterologist.[103] A large, retrospective, nonrandomized, observational cohort study examined 1.38 million procedures including upper endoscopy and colonoscopy. The authors of this study concluded that the use of anesthesiology professionals in ASA 1 or ASA 2 patients undergoing colonoscopy was associated with a lower incidence of serious adverse events (0.20%) as compared to sedation provided by endoscopists (0.28%). Interestingly, they found that the incidence of serious adverse events with upper endoscopy was lower with endoscopist-led sedation as compared to sedation provided by anesthesia professionals. However, the study authors admitted limitations given the retrospective nature of the study. All serious adverse events might not have been documented, and decisions about the use of anesthesia professionals might have been affected by complexity of the procedure or patient.[104]

Despite the low incidence of adverse events, the anesthesiologist should anticipate that complications will occasionally occur when administering sedation for GI endoscopy.[105,106] The general principles for management of these complications is the same as for cases performed in the OR; however, the resources available to aid the provider can be limited in the endoscopy suite. While the support personnel in the OR may be comfortable assisting the anesthesiologist during episodes of patient

decompensation, nursing staff in the endoscopy center may not be able to provide the same level of assistance. In addition, equipment that is readily accessible in the OR, such as that needed for advanced airway management, may not be immediately available in the endoscopy area. These limitations put special importance on adequate preparation for each case. Any special equipment that might be required should be brought to the anesthetizing location and made ready for use before the case begins. Additionally, a plan to obtain additional assistance should be in place should a serious adverse event occur. If a patient is of sufficiently high risk, it may be advisable to perform the procedure in the OR, where serious complications can be dealt with in a more efficient manner.

Postanesthesia Recovery

The anesthesiologist must fully appreciate the capabilities of the nursing staff responsible for monitoring patients after endoscopy. GI endoscopy units are often staffed to provide nursing care at the level necessary to recover patients who have received moderate sedation. However, it is essential that patients who have received deep sedation or general anesthesia in the endoscopy suite receive the same level of recovery care they would receive in the postanesthesia care unit of the OR. Accrediting organizations such as The Joint Commission require that equivalent postanesthesia care be delivered in all locations within the health care center. Determining whether an equivalent level of postprocedure patient care can be provided in the endoscopy center depends on whether nursing staff in the endoscopy recovery unit have received similar training as the nurses in the surgical postanesthesia care unit and also whether the appropriate nurse-patient ratio can be maintained. If the anesthesia provider is not comfortable with the level of postprocedure care offered for a particular patient, the patient should be transferred to the surgical recovery unit.

Discharge criteria should be the same as those used for patients who have been anesthetized in the OR. Recovery nurses must understand these criteria and also must know how to reach anesthesia personnel should issues arise during the recovery period. Postanesthesia management of patients with obstructive sleep apnea may be especially challenging as they may require an extended period of monitoring before satisfying criteria for discharge, which include maintaining an acceptable oxygen saturation while breathing room air. If staffing issues in the endoscopy recovery area do not allow such extended monitoring, arrangements should be made for recovery in a more suitable location.

References

1. Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol*. 2006;101:967–974.

2. Clergue F. The challenges of anaesthesia for the next decade: the Sir Robert Macintosh Lecture 2014. *Eur J Anaesthesiol*. 2015;32:223–229.

3. McCloy R, Nagengast F, Fried M, et al. Conscious sedation for endoscopy. *Eur J Gastroenterol Hepatol*. 1996;8:1233–1240.

4. Heuss LT, Schnieper P, Drewe J, et al. Risk stratification and safe administration of propofol by registered nurses supervised by the gastroenterologist: a prospective observational study of more than 2000 cases. *Gastrointest Endosc*. 2003;57:664–671.

5. Rex DK, Heuss LT, Walker JA, et al. Trained registered nurses/ endoscopy teams can administer propofol safely for endoscopy. *Gastroenterology*. 2005;129:2080–2083.

6. Rex KD, Overley CA, Walker J. Registered nurse-administered propofol sedation for upper endoscopy and colonoscopy: why? when? how? *Rev Gastroenterol Dis*. 2003;3:70–80.

7. Campo R, Brullet E, Montserrat A, et al. Identification of factors that influence tolerance of upper gastrointestinal endoscopy. *Eur J Gastroenterol Hepatol*. 1999;11:201–204.

8. Shingina A, Ou G, Takach O, et al. Identification of factors associated with sedation tolerance in 5000 patients undergoing outpatient colonoscopy: Canadian tertiary center experience. *World J Gastrointest Endosc*. 2016;8:770–776.

9. Braunstein ED, Rosenberg R, Gress F, et al. Development and validation of a clinical prediction score (the SCOPE score) to predict sedation outcomes in patients undergoing endoscopic procedures. *Aliment Pharmacol Ther*. 2014;40:72–82.

10. Chang B, Urman RD. Non-operating room anesthesia: the principles of patient assessment and preparation. *Anesthesiol Clin*. 2016;34(1):223–240.

11. Pike IM: Open-access endoscopy. *Gastrointest Endosc Clin N Am*. 2006;16:709–717.

12. Mathew A, Riley TR 3rd, Young M, et al. Cost-saving approach to patients on long-term anticoagulation who need endoscopy: a decision analysis. *Am J Gastroenterol*. 2003;98:1766–1776.

13. Hussain N, Alsulaiman R, Burtin P, et al. The safety of endoscopic sphincterotomy in patients receiving antiplatelet agents—a case-control study. *Aliment Pharmacol Ther*. 2007;25:579–584.

14. Kanakadandi V, Parasa S, Sihn P, et al. Patterns of antiplatelet agent use in the US. *Endosc Int Open*. 2015;3:E173–E178.

15. Aisenberg J, Brill JV, Ladabaum U, et al. Sedation for gastrointestinal endoscopy: new practices, new economics. *Am J Gastroenterol*. 2005;100:996–1000.

16. Savarise MT. Coding and reimbursement for colonoscopy. *Bull Am Coll Surg*. 2016;101:40–43.

17. Centers for Medicare and Medicaid Services, HHS. Medicare program; revisions to payment policies under the Physician Fee Schedule, Clinical Laboratory Fee Schedule, access to identifiable data for the Center for Medicare and Medicaid innovation models and other revisions to Part B for CY 2015. *Fed Regist*. 2014, November 13; 79(219):67547–68010.

18. Cohen LB, Delegge MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. *Gastroenterology*. 2007;133:675–701.

19. Vargo JJ, Bramley T, Meyer K, et al. Practice efficiency and economics: the case for rapid recovery sedation agents for colonos-copy in a screening population. *J Clin Gastroenterol*. 2007;41:591–598.

20. Trummel J. Sedation for gastrointestinal endoscopy: the changing landscape. *Curr Opin Anaesthesiol*. 2007;20:359–364.

21. United States Food and Drug Administration. Propofol product label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019627s062lbl.pdf. Accessed on March 9, 2018.

22. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology*. 2002;96:1004–1017.

23. Rex DK, Deenadayalu VP, Eid E, et al. Endoscopist-directed administration of propofol: a worldwide safety experience. *Gastroenterology*. 2009;137:1229–1237.

24. Fatima H, DeWitt J, LeBlanc J, et al. Nurse-administered propofol sedation for upper endoscopic ultrasonography. *Am J Gastroenterol*. 2008;103:1649–1656.

25. Dewitt J, McGreevy K, Sherman S, et al. Nurse-administered propofol sedation compared with midazolam and meperidine for EUS: a prospective, randomized trial. *Gastrointest Endosc*. 2008;68:499–509.

26. Cohen LB. Nurse-administered propofol sedation for upper endoscopic ultrasonography: not yet ready for prime time. *Nat Clin Pract Gastroenterol Hepatol*. 2009;6:76–77.

27. Goudra BG, Singh PM, Gouda G, et al. Safety of non-anesthesia provider-administered propofol (NAAP) sedation in advanced

gastrointestinal endoscopic procedures: comparative meta-analysis of pooled results. *Dig Dis Sci*. 2015;60:2612–2627.

28. Dumonceau J, Riphaus A, Schreiber F, et al. Non-anesthesiologist administration of propofol for gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates Guideline–updated June 2015. *Endoscopy*. 2015;47:1175–1189.

29. Crepeau T, Poincloux L, Bonny C, et al. Significance of patient-controlled sedation during colonoscopy. Results from a prospective randomized controlled study. *Gastroenterol Clin Biol*. 2005;29:1090–1096.

30. Mandel JE, Tanner JW, Lichtenstein GR, et al. A randomized, controlled, double-blind trial of patient-controlled sedation with propofol/remifentianil versus midazolam/fentanyl for colonoscopy. *Anesth Analg*. 2008;106:434–439.

31. Manzanikov M, Udd M, Kylanpaa L, et al. A randomized comparison of target-controlled propofol infusion and patient-controlled sedation during ERCP. *Endoscopy*. 2013;45:915–919.

32. Manzanikov M, Udd M, Kylanpaa L, et al. Dexmeditomidine impairs success of patient-controlled sedation in alcoholics during ERCP: a randomized, double-blind, placebo-controlled study. *Surg Endosc*. 2013;27:2163–2168.

33. Maurice-Szamburski A, Loundou A, Auquier P, et al. Effecto of patient-controlled sedation with propofol on patient satisfaction: a randomized study. *Ann Fr Anesth Reanim*. 2013;32:171–175.

34. Nguyen NQ, Toscano L, Lawrence M, et al. Patient-controlled analgesia with inhaled methoxyflurane versus conventional endoscopist-provided sedation for colonoscopy: a randomized multicenter trial. *Gastrointest Endosc*. 2013;78:892–901.

35. Manzanikov M, Udd M, Kylanpaa L, et al. Patient-controlled sedation with propofol and remifentanil for ERCP: a randomized, controlled study. *Gastrointest Endsoc*. 2011;73:260–266.

36. Kulling D, Fantin AC, Biro P, et al. Safer colonoscopy with patient-controlled analgesia and sedation with propofol and alfentanil. *Gastrointest Endosc*. 2001;54:1–7.

37. Ng JM, Kong CF, Ny MD. Patient-controlled sedation with propofol for colonoscopy. *Gastrointest Endosc*. 2001;54:8–13.

38. Crepeau T, Poincloux L, Bonny C, et al. Significance of patient-controlled sedation during colonoscopy. Results from a prospective randomized controlled study. *Gastroenterol Clin Biol*. 2005;29:1090–1096.

39. Fanti L, Rossi G, Gemma M, et al. Target controlled infusion for non-anaesthesiologist propofol sedation during gastrointestinal endoscopy: the first double blind randomized controlled trial. *Gastrointest Endosc*. 2015;47(7):566–571.

40. Seo SI, Ryu JY, Kang SS. Safety of target-controlled propofol infusion by gastroenterologists in patients undergoing endoscopic resection. *Dig Dis Sci*. 2016;61:3199–3206.

41. Urman RD, Maurer WG. Computer-assisted personalized sedation: friend or foe? *Anesth Analg*. 2014;119(1):207–211.

42. Periello B. Johnson & Johnson bails on Sedasys anesthesia device. *Mass Device*. March 15, 2016. Available at: http://www.massdevice.com/johnson-johnson-bails-sedasys-automated-anesthesia-device/. Accessed on January 7, 2017.

43. Aantaa R, Scheinin M. Alpha 2-adrenergic agents in anaesthesia. *Acta Anaesthesiol Scand*. 1993;37:433–448.

44. Shelly MP. Dexmedetomidine: a real innovation or more of the same? *Br J Anaesth*. 2001;87:677–678.

45. Demiraran Y, Korkut E, Tamer A, et al. The comparison of dexmedetomidine and midazolam used for sedation of patients during upper endoscopy: a prospective, randomized study. *Can J Gastroenterol*. 2007;21:25–29.

46. Wu W, Chen Q, Zhang LC, Chen WH. Dexmedetomidine versus midazolam for sedation in upper gastrointestinal endoscopy. *J Int Med Res*. 2014;42:516–522.

47. Jalowiecki P, Rudner R, Gonciarz M, et al. Sole use of dexmedetomidine has limited utility for conscious sedation during outpatient colonoscopy. *Anesthesiology*. 2005;103:269–273.

48. Wu Y, Zhang Y, Hu X, et al. A comparison of propofol vs. dexmedetomidine for sedation, haemodynamic control and satisfaction, during esophagogastroduodenoscopy under conscious sedation. *J Clin Pharm Ther*. 2015;40:419–425.

49. Vadivelu N, Schermer E, Kodumudi V, Belani K, Urman RD, Kaye AD. Role of ketamine for analgesia in adults and children. *J Anaesthesiol Clin Pharmacol*. 2016;32(3):298–306.

50. White PF, Way WL, Trevor AJ. Ketamine-its pharmacology and therapeutic uses. *Anesthesiology*. 1982;56:119–136.

51. Gilger MA, Spearman RS, Dietrich CL, et al. Safety and effectiveness of ketamine as a sedative agent for pediatric GI endoscopy. *Gastrointest Endosc*. 2004;59:659–663.

52. Law AK, Ng DK, Chan KK. Use of intramuscular ketamine for endoscopy sedation in children. *Pediatr Int*. 2003;45:180–185.

53. Kirberg A, Sagredo R, Montalva G, et al. Ketamine for pediatric endoscopic procedures and as a sedation complement for adult patients. *Gastrointest Endosc*. 2005;61:501–502.

54. Varadarajulu S, Eloubeidi MA, Tamhane A, et al. Prospective randomized trial evaluating ketamine for advanced endoscopic procedures in difficult to sedate patients. *Aliment Pharmacol Ther*. 2007;25:987–997.

55. Keeffe EB, O'Connor KW. 1989 A/S/G/E survey of endoscopic sedation and monitoring practices. *Gastrointest Endosc*. 1990;36:S13.

56. Mamula P, Markowitz J, Neiswender K, et al. Safety of intravenous midazolam and fentanyl for pediatric endoscopy: prospective study of 1578 endoscopies. *Gastrointest Endosc*. 2007;65:203–210.

57. Litman RS. Conscious sedation with remifentanil during painful medical procedures. *J Pain Symptom Manage*. 2000;19:468–471.

58. Wesolowski AM, Zaccagnino MP, Malapero RJ, Kaye AD, Urman RD. Remimazolam: pharmacologic considerations and clinical role in anesthesiology. *Pharmacotherapy*. 2016;36(9):1021–1027.

59. Rogers WK, McDowell TS. Remimazolam, a short-acting GABA(A) receptor agonist for intravenous sedation and/or anesthesia in day-case surgical and non-surgical procedures. *IDrugs*. 2010;13:929–937.

60. Pambiano DJ, Cash BD. New horizons for sedation: The ultrashort acting benzodiazepine remimazolam. *Tech Gastrointest Endosc*. 2016;18:22–28.

61. Patel S, Vargo JJ, Khandwala F, et al. Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. *Am J Gastroenterol*. 2005;100:2689–2695.

62. Lopez-Gil M, Brimacombe J, Diaz-Reganon G. Anesthesia for pediatric gastroscopy: a study comparing the ProSeal laryngeal mask airway with nasal cannulae. *Paediatric Anaesthia*. 2006;16:1032–1035.

63. Davis DE, Jones MP, Kubik CM. Topical pharyngeal anesthesia does not improve upper gastrointestinal endoscopy in conscious sedated patients. *Am J Gastroenterol*. 1999;94:1853–1856.

64. Ristikankare M, Hartikainen J, Heikkinen M, et al. Is routine sedation or topical pharyngeal anesthesia beneficial during upper endoscopy? *Gastrointest Endosc*. 2004;60:686–694.

65. Evans LT, Saberi S, Kim HM, et al. Pharyngeal anesthesia during sedated EGDs: is “the spray” beneficial? A meta-analysis and systematic review. *Gastrointest Endosc*. 2006;63:761–766.

66. Byrne MF, Mitchell RM, Gerke H, et al. The need for caution with topical anesthesia during endoscopic procedures, as liberal use may result in methemoglobinemia. *J Clin Gastroenterol*. 2004;38:225–229.

67. Ayoub C, Skoury A, Abdul-Baki H, et al. Lidocaine lollipop as single-agent anesthesia in upper GI endoscopy. *Gastrointest Endosc*. 2007;66:786–793.

68. Chen SC, Rex DK. An initial investigation of bispectral monitoring as an adjunct to nurse-administered propofol sedation for colonoscopy. *Am J Gastroenterol*. 2004;99:1081–1086.

69. Moerman AT, Foubert LA, Herregods LL, et al. Propofol versus remifentanil for monitored anaesthesia care during colonoscopy. *Eur J Anaesthesiol*. 2003;20:461–466.

70. Akcaboy ZN, Akcaboy EY, Albayrak D, et al. Can remifentanil be a better choice than propofol for colonoscopy during monitored anesthesia care? *Acta Anaesthesiol Scand*. 2006;50:736–741.

71. Theodorou T, Hales P, Gillespie P, et al. Total intravenous versus inhalational anaesthesia for colonoscopy: a prospective study of clinical recovery and psychomotor function. *Anaesth Intensive Care*. 2001;29:124–136.

72. VanNatta ME, Rex DK. Propofol alone titrated to deep sedation versus propofol in combination with opioids and/or benzodiazepines and titrated to moderate sedation for colonoscopy. *Am J Gastroenterol*. 2006;101:2209–2217.

73. Gurbulak B, Uzman S, Kabul Gurbulak E, et al. Cardiopulmonary safety of propofol versus midazolam/meperidine sedation for colonoscopy: a prospective, randomized, double-blinded study. *Iran Red Crescent Med J*. 2014;16:e19329.

74. Fisher L, Fisher A, Thomson A. Cardiopulmonary complications of ERCP in older patients. *Gastrointest Endosc*. 2006;63:948–955.

75. Coté GA, Hovis RM, Ansstas MA, et al. Incidence of sedation-related complications with propofol use during advanced endoscopic procedures. *Clin Gastroenterol Hepatol*. 2010;8:137–142.

76. Lordan JT, Woods J, Keeling P, Paterson IM. A retrospective analysis of benzodiazepine sedation vs. propofol anaesthesia in 252 patients undergoing endoscopic retrograde cholangiopancreatography. *HPB (Oxford)*. 2011;13:174–177.

77. Goyal R, Hasnain S, Mittal S, Shreevastava S. A randomized, controlled trial to compare the efficacy and safety profile of a dexmedetomidine-ketamine combination with a propofol-fentanyl combination for ERCP. *Gastrointest Endosc*. 2016;83:928–933.

78. Jung M, Hofmann C, Kiesslich R, et al. Improved sedation in diagnostic and therapeutic ERCP: propofol is an alternative to midazolam. *Endoscopy*. 2000;32:233–238.

79. Fanti L, Agostoni M, Casati A, et al. Target-controlled propofol infusion during monitored anesthesia in patients undergoing ERCP. *Gastrointest Endosc*. 2004;60:361–366.

80. Raymondos K, Panning B, Bachem I, et al. Evaluation of endoscopic retrograde cholangiopancreatography under conscious sedation and general anesthesia. *Endoscopy*. 2002;34:721–726.

81. Martindale SJ. Anaesthetic considerations during endoscopic retrograde cholangiopancreatography. *Anaesth Intensive Care*. 2006;34:475–480.

82. Osborn IP, Cohen J, Soper RJ, et al. Laryngeal mask airway—a novel method of airway protection during ERCP: comparison with endotracheal intubation. *Gastrointest Endosc*. 2002;56:122–128.

83. Hagan K, Ruiz J, Thirumurthi S, et al. Total intravenous anesthesia without an endotracheal tube for endoscopic retrograde cholangiopancreatography and the incidence of conversion to endotracheal intubation: a retrospective review. *Gastrointest Endosc.* 2015;81:AB308.

84. Fanti L, Agostoni M, Arcidiacono PG, et al. Target-controlled infusion during monitored anesthesia care in patients undergoing EUS: propofol alone versus midazolam plus propofol. A prospective double-blind randomised controlled trial. *Dig Liver Dis*. 2007;39:81–86.

85. Agostoni M, Fanti L, Arcidiacono PG, et al. Midazolam and pethidine versus propofol and fentanyl patient controlled sedation/analgesia for upper gastrointestinal tract ultrasound endoscopy: a prospective randomized controlled trial. *Dig Liver Dis*. 2007;39:1024–1029.

86. Ootaki C, Stevens T, Vargo J, et al. Does general anesthesia increase the diagnostic yield of endoscopic ultrasound-guided fine needle aspiration of pancreatic masses: *Anesthesiology*. 2012;117:1044–1050.

87. Ko CW, Kalloo AN. Per-oral transgastric abdominal surgery. *Chinese J Digest Dis*. 2006;7:67–70.

88. Pai RD, Fong DG, Bundga ME, et al. Transcolonic endoscopic cholecystectomy; a NOTES survival study in a porcine model. *Gastrointest Endosc*. 2006;64:428–434.

89. Kantsevoy SV, Jagannath SB, Niiyama H, et al. Endoscopic gastrojejunostomy with survival in a porcine model. *Gastrointest Endosc*. 2005;62:287–292.

90. Jagannath SB, Kantsevoy SV, Vaughn CA, et al. Peroral transgas-tric endoscopic ligation of fallopian tubes with long-term survival in a porcine model. *Gastrointest Endosc*. 2005;61:449–453.

91. Kantsevoy SV, Hu B, Jagannath SB, et al. Transgastric endoscopic splenectomy: is it possible? *Surg Endosc*. 2006;20:522–525.

92. Marescaux J, Dallemagne B, Peretta S, et al. Surgery without scars: report of translumenal cholecystectomy in a human being. *Arch Surg*. 2007;142:823–826.

93. Zorron R, Maggioni LC, Pombo L, et al. NOTES transvaginal cholecystectomy: preliminary clinical application. *Surg Endosc*. 2008;22:542–547.

94. Ramos AC, Murakami A, Galvao Neto M, et al. NOTES trans-vaginal video-assisted cholecystectomy: first series. *Endoscopy*. 2008;40:572–575.

95. Auyang ED, Hungness ES, Vaziri K, et al. Human NOTES cholecystectomy: transgastric hybrid technique. *J Gastrointest Surg*. 2009;13:1149–1150.

96. Clark MP, Qayed ES, Kooby DA, et al. Natural orifice transluminal endoscopic surgery in humans: a review. *Minim Invasive Surg*. 2012;2012:189296.

97. Marks JM, Ponsky JL, Pearl JP, McGee MF. PEG “rescue”: a practical NOTES technique. *Surg Endosc*. 2007;21:816–819.

98. Pearl JP, Ponsky JL. Natural orifice translumenal endoscopic surgery: a critical review. *J Gastrointest Surg*. 2008;12:1293–1300.

99. Hamad MA, El-Khattary OA Ibrahim, et al. Laparoscopic cholecystectomy under spinal anesthesia with nitrous oxide peritoneum: a feasibility study. *Surg Endosc*. 2003;17:1426–1428.

100. Hammer GB, Litalien C, Wellis V, et al. Determination of the median effective concentration (EC50) of propofol during oesophagogastroduodenoscopy in children. *Paediatr Anaesth*. 2001;11:549–553.

101. Paspatis GA, Charoniti I, Manolaraki M, et al. Synergistic sedation with oral midazolam as a premedication and intravenous propofol versus intravenous propofol alone in upper gastrointestinal endoscopies in children: a prospective, randomized study. *J Pediatr Gastroenterol Nutr*. 2006;43:195–199.

102. Akbulut UE, Saylan S, Sengu B, et al. A comparison of sedation with midazolam-ketamine versus propofol-fentanyl during endoscopy in children: a randomized trial. *Eur J Gastroenterol Hepatol*. 2017;29:112–118.

103. Vargo JJ, Holub JL, Faigel DO, et al. Risk factors for cardiopulmonary events during propofol-mediated upper endoscopy and colonoscopy. *Aliment Pharmacol Ther*. 2006;24:955–963.

104. Vargo JJ, Niklewski PJ, Williams JL, et al. Patient safety during sedation by anesthesia professionals during routine upper endoscopy and colonoscopy: an analysis of 1.38 million procedures. *Gastrointest Endosc*. 2017;85:101–108.

105. Chang B, Kaye AD, Diaz JH, Westlake B, Dutton RP, Urman RD. Complications of non-operating room procedures: outcomes from the national anesthesia clinical outcomes registry. *J Patient Saf*. 2015. [Epub ahead of print].

106. Woodward ZG, Urman RD, Domino KB. Safety of non-operating room anesthesia: a closed claims update. *Anesthesiol Clin*. 2017;35(4):569–581.