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EDITORIAL

Propofol use in endoscopic retrograde cholangiopancreatography and endoscopic ultrasound

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Abstract

Compared to standard endoscopy, endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) are often lengthier and more complex, thus requiring higher doses of sedatives for patient comfort and compliance. The aim of this review is to provide the reader with information regarding the use, safety profile, and merits of propofol for sedation in advanced endoscopic procedures like ERCP and EUS, based on the current literature.

Key words: Propofol; Endoscopy; Ndoscopic retrograde cholangiopancreatography; Endoscopic ultrasound; Safety

Core tip: There is a plethora of data to support the safety profile of propofol in general endoscopy, and many studies that support non-anesthesiologist administered propofol. There are also compelling data that support its use in endoscopic retrograde cholangiopancreatography and endoscopic ultrasound. In the world of advanced therapeutic endoscopy, where patient burden, risk, and cost are high, propofol based sedation delivered by non-anesthetic, but appropriately trained individuals, should become the new standard.

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INTRODUCTION

Propofol is an ultra-short acting hypnotic agent with no analgesic properties that acts quickly and efficaciously to sedate patients. The food and drug administration have approved its use for the induction and maintenance of anesthesia, and also recommend that individuals with training in general anesthesia should administer it[1]. Historically, propofol delivered by anesthetists for endoscopic procedures is considered to be a safe but costly practice. In the setting of increasing financial burdens on health care systems, alternatives need to be addressed.

The use of moderate, or "conscious" sedation with benzodiazepines and analgesics for routine endoscopic procedures such as esophagogastroduodenoscopy (EGD) and colonoscopy is well established, and generally accepted by patients and endoscopists. With advancements in endoscopic technology and expertise however, therapeutic procedures are becoming increasingly complex. Advancing age and co-morbidity also seems to be less of a deterrent for endoscopic therapy, particularly when alternatives may involve general anesthesia and surgical intervention.

Compared to standard endoscopy, endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) are often lengthier and more complex, thus requiring higher doses of sedatives for patient comfort and compliance[2]. Naturally this may increase risk

Table 1 Characteristics of commonly used pharmacological agents used during endoscopy

Agent	Onset of action (min)	Duration of action	Half life	Metabolism
Midazolam	1.0-2.5	2-6 h	1.8-6.4 h	Hepatic and intestinal
Fentanyl	< 1.5	1-2 h	2-7 h	Hepatic
Meperidine	5	2-4 h	2-7 h	Hepatic
Propofol	> 1	3-10 min	Triphasic: 2.2 min, 20 min, 8 h	Hepatic

Modified from Triantafillidis *et al*[30].

of sedation related complication along with prolonged recovery times.

The aim of this review is to provide the reader with information regarding the use, safety profile, and merits of propofol sedation in advanced endoscopic procedures like ERCP and EUS, based on the current literature.

PROPOFOL IN GENERAL ENDOSCOPY

Propofol is 98% plasma protein bound and highly lipophilic, which enables it to cross the blood-brain barrier easily. This results in both a rapid onset of action and short half-life as it redistributes into peripheral tissues quickly. It delivers rapid sedation compared to benzodiazepines and opiates, and has a shorter recovery profile, see Table 1. Although it has a rapid onset of action and short half-life, propofol also has a relatively narrow therapeutic index, which carries a greater potential for complication, particularly if administered by inexperienced individuals.

There is no doubt, however, that the use of standard, conscious sedation with benzodiazepines and opiates is not always ideal. Virtually every endoscopist will have had the experience of administering medication and performing a procedure on a sub-optimally sedated patient, only to have them sleep deeply afterwards. This usually results from the procedure starting before the medication is in full effect, followed by "top-up" medication given in an attempt to placate the struggling individual. This may result in delayed sedation, cardio-respiratory compromise and delayed discharge from the endoscopy unit. A prospective, randomized study has shown that not only were patient and endoscopists more satisfied with propofol compared to standard sedation practices, but that they have significantly shorter recovery times and quicker return to baseline activities and diet[3].

PROPOFOL: SAFETY PROFILE

For the last three decades, the use of propofol during endoscopic procedures in non-ventilated patients has been increasing. In a world-wide safety review by Rex *et al*[4] in 2009, over 646000 cases, of which approximately 220000 were published, the incidence of adverse events related to propofol use during endoscopy was comparable to published data on general anesthesia administered by anesthetists. The incidence of bag-mask ventilation during this review was 0.1%, and a total of 11 out of 646000 cases required endotracheal intubation, of which 7 quickly recovered and 4 died. The 4 patients that died each had significant co-morbidity including severe mental retardation and advanced malignancy. From this extensive review, the overall mortality rate for endoscopist directed administration of propofol would be 1 in 161515 cases[4]. Interestingly, the published safety profiles of benzodiazepine and opiate use for conscious sedation during endoscopy is worse, with a recent retrospective review of 324727 cases showing 39 deaths (11 per 100000)[5]. The data from older studies is even more disconcerting, with mortality rates of up to 1 in 1000[6].

Nonanesthesiologist-administered propofol (NAAP) during endoscopy describes the drug either as a single agent or in combination with benzodiazepines and opiates being given by a physician who has not been trained as an anesthesiologist. Nurse-administered propofol sedation (NAPS) is typically the administration of propofol as a single agent by a nurse, under physician direction. Several published studies regarding safety profiles use a combination of both practices and show reproducible safety profiles. Cohen *et al*[7] in 2003 published a retrospective review of over 800 consecutive endoscopies during which propofol was administered in conjunction with small doses of midazolam and meperidine under the direction of a gastroenterologist. None of the patients required pharmacological reversal or mechanical ventilation during or after the procedure. Another study by Rex *et al*[8] evaluated over 2000 endoscopic procedures during which propofol was administered by nurses under the direction of an endoscopist. 4 patients required brief mask ventilation for low oxygen saturations, but no patients required endotracheal intubation or suffered long-term sequelae from propofol administration.

A systematic review and meta-analysis of 36 randomized, controlled trials of moderate sedation for routine endoscopic procedures found no difference in adverse events between midazolam plus narcotics and propofol[9]. Coté *et al*[10] identified that male sex, raised Body mass index (BMI), and American Association of Anesthesiologist (ASA) class Ⅲ or higher were independent predictors of requirement of airway manoeuvres. During complex procedures, it may be challenging to adequately monitor the patient's respiratory rate for signs of apnea. Capnographic monitoring of end tidal carbon dioxide can potentially detect subtle changes in respiratory status before peripheral pulse oximetry. Qadeer *et al*[11] showed that capnographic monitoring during ERCP and EUS reduced the frequency of hypoxemia and apnea.

Monitored anesthetic care (MAC) during endoscopy involves specialist care provided by a trained anesthesiologist, and may involve deep sedation. This spectrum may encompass general anesthesia requiring endotracheal intubation. As evidenced by the aforementioned studies, the rate of complication from NAAP during endoscopy

Table 2 American Society of Gastrointestinal Endoscopy training guidelines for nonanesthesiologist-administered propofol for gastrointestinal endoscopy

Didactic training
Pharmacological overview of propofol
Review of continuum of sedation
Patient assessment specific to propofol
Examination
Airway workshop
Training to recognize and manage respiratory complications
Airway assessment
Restore airway patency with manual, oral or nasopharyngeal techniques
Bag-mask ventilation
Basic and advanced cardiac life support
Review of physiologic monitoring techniques (capnography)
Simulation training
Clinical simulators with trained instructors
Preceptorship
Adopt and institute a propofol sedation program within endoscopy unit
Formulate set of policies and procedures pertaining to NAAP
Train all relevant members of staff
Institutional approval
Performance measures designed to assess patient safety and satisfaction

Adapted from Vargo *et al*[28]. NAAP: Nonanesthesiologist-administered propofol.

appears so low that the benefit of MAC is negligible in routine endoscopy[12]. The American Society of Gastrointestinal Endoscopy (ASGE) guidelines on NAAP recommend appropriate training in order to ensure competence and maximise safety, see Table 2.

BALANCED PROPOFOL SEDATION

Using propofol in combination with benzodiazepines and opiates may reduce the amount of propofol required to provide a satisfactory level of sedation and thereby reduce adverse events. An Italian study of over 1500 consecutive patients undergoing diagnostic colonoscopies with non-anesthesiologist administered propofol and midazolam demonstrated that concurrent administration yielded moderate sedation with relatively small doses of propofol (median 70 mg, range: 40-120 mg)[13]. A prospective, randomized study from Greece evaluated 120 consecutive patients undergoing colonoscopy. 64 patients were randomized to midazolam and propofol, and 56 received midazolam and pethidine. A multivariate logistic regression analysis demonstrated that the only factor that improved both patient comfort and recovery time was synergistic sedation with midazolam and propofol[14]. This outcome was also seen in a study by Levitzky *et al*[15], who demonstrated that balanced propofol sedation targeted to moderate sedation, administered by trained endoscopists during EGD, resulted in superior patient satisfaction and shorter recovery times.

A randomized, double-blind study from Korea however, demonstrated that propofol monosedation appeared to be as effective to balanced sedation practices. This comprehensive study of over 200 patients undergoing ERCP or EUS showed significantly shorter recovery times with propofol (13.4 ± 6.24 min) compared to propofol with midazolam and fentanyl (18.37 ± 7.86 min). Patient satisfaction, tolerance, recollection of the procedure or experience of pain did not differ between the groups[16]. This data demonstrates that propofol monosedation, administered effectively by trained personnel, may be a viable practice.

PROPOFOL FOR ERCP

ERCP is a technically challenging and unique modality to diagnose and therapeutically manage disorders of the pancreas and biliary tract. Over the last five decades, ERCP has progressed from a diagnostic aid to the mainstay for management of complex stone disease along with benign and malignant strictures. Despite the use of conscious sedation with benzodiazepines and opiates, this procedure can be time consuming, painful, and difficult for patients to endure. ERCP also requires patient cooperation during critical junctures such as cannulation, sphincterotomy and complex stent placement. Poor cooperation may result in increased risk of complications or failed procedures. In an effort to settle a patient, endoscopists may request for more sedation or analgesia to be given, potentially increasing the risk of sedation related complication. Patel *et al*[2] showed that ERCP is an independent risk factor for deep sedation in elective endoscopy.

Patients with chronic biliary disease such as primary sclerosing cholangitis may also undergo multiple procedures highlighting the importance of making it bearable. A study from The Netherlands demonstrated that nearly 50% of patients undergoing ERCP for a variety of indications experience pain and discomfort during and immediately after ERCP. Younger age was also a factor for significantly increased patient discomfort[17].

A prospective, controlled study of 198 consecutive patients undergoing ERCP with midazolam or propofol for sedation concluded that propofol was safe, more effective for sedation with higher patient cooperation, and had significantly shorter recovery times[18]. A Cochrane database review of 124 papers and 4 randomized controlled trials performed by Garewal *et al*[19] concluded that patients who underwent ERCP with midazolam and meperidine had longer recovery times and no less adverse events than those who had the procedure with propofol. This review, however, was limited by the fact that data on anesthesia involvement in propofol administration was not clear.

Elderly patients who undergo advanced endoscopic procedures may be at greater risk of adverse events related to sedation. With an aging population and more access to endoscopic services; however, ERCP is commonly performed in this cohort of individuals. A randomized, controlled study from Germany evaluated the use of

propofol in 150 consecutive patients aged over 80. These patients were considered to be high risk with at least 91% of them being ASA grade Ⅲ or higher. Half of the patients were randomized to midazolam plus meperidine, and half to propofol alone. The group who received propofol demonstrated significantly higher levels of cooperation, shorter recovery times, and significantly lower number of desaturation events[20].

Patient controlled sedation is an evolving area in therapeutic endoscopy. A recent Finnish randomized comparison study of target-controlled propofol infusion to patient controlled sedation during ERCP demonstrated that the latter group required less propofol and recovered faster. In this study, 82 patients undergoing elective ERCP were randomized to receive propofol as a target controlled infusion (target effective- site concentration of 2 μg/mL) or patient controlled administration (1 mL of propofol administered whenever patient pressed the button, with no lock out period). Patients with a history of alcohol abuse, substance abuse, and those with an ASA > Ⅲ were excluded. An anesthesiologist was present during the procedures. There were no significant differences in patient experience, satisfaction, sedation preference, or endoscopist evaluation of the procedure, however recovery time was significantly shorter in the patient controlled sedation group (5 ± 6 min, *vs* 10 ± 13 min)[21].

PROPOFOL FOR EUS

Endoscopic ultrasound is a highly effective, increasingly utilized modality to assess gastrointestinal (GI) pathology. Pancreatic cysts are frequently found on other imaging studies and referred for EUS and potential fine needle aspiration (FNA). While routine diagnostic EUS carries relatively low risk, it generally is more time consuming and potentially more uncomfortable than a diagnostic EGD. Procedures that involve intentional visceral puncture with a needle, such as FNA or celiac plexus block, require that a patient be cooperative. The same is true for more advanced, therapeutic EUS guided procedures such as cyst gastrostomy and necrosectomy.

Yusoff *et al*[22] studied 500 prospective patients who received propofol administered by a trained endoscopist. Patients who were ASA Ⅲ and above were excluded. No procedural complications were encountered and all patients stated that they would prefer the same method of sedation for repeat procedures. Another study from Spain specifically investigated the use of propofol for EUS in average to high-risk patients. This prospective observational study of 446 patients included 138 high-risk individuals with an ASA of Ⅲ-Ⅳ. A trained nurse under the direction of the endoscopist administered propofol, and no procedural related complications were noted[23]. A further study of 112 patients who underwent EUS with FNA with BPS showed no significant sedation related complications. This study, however, involved two gastroenterologists per procedure; one to perform the EUS, and one to administer the propofol[24].

Currently there are no studies which evaluate the use of propofol or BPS compared to standard sedation practices in complex procedures such as EUS guided necrosectomy and cyst gastrostomy. Given the wealth of evidence supporting the safety profile of propofol in other endoscopic procedures, its use is justified, with the caveat that these patients may have added co-morbidity, possibly requiring the supervision of anesthetic personnel.

PROPOFOL: ADMINISTRATION

Protocols for propofol administration will vary between centers, however most published data have similar guidelines. One study which compared bolus propofol administration to continuous infusion outlines an initial bolus depending on body weight (< 70 kg: 40 mg; > 70 kg: 60 mg), followed by 10-20 mg bolus doses as required. The continuous infusion group had an initial bolus of 1 mg/kg, followed by an infusion of 6 mg/kg. Patients in both groups also received an initial bolus of midazolam 3 mg. No differences were noted in patient experience, however recovery was signifantly longer in the infusion group[25].

PROPOFOL: COST EFFECTIVE?

Cost and efficiency are two potentially conflicting entities. There are several studies which demonstrate more rapid induction of sedation and faster recovery with propofol compared to standard sedation. Dewitt *et al*[26] evaluated the utility of NAPS compared to midazolam and meperidine for EUS in an outpatient setting. Compared to standard sedation, NAPS for EUS had a significantly faster induction of sedation, full recovery time, patient satisfaction and similar total cost to perform. In 2002, Vargo came to similar conclusions that propofol delivered by a registered nurse would reduce cost compared to physician administration[3]. Given the weight of evidence that supports the safety profile of NAAP, it now seems unnecessary to consider the financial implication of MAC, which may be significant depending on institution and country[27]. The American Society of Gastrointestinal Endoscopy (ASGE) position statement recommends that NAAP is more cost effective than standard sedation for ERCP and EUS, based on a high grade (IB) of evidence[28].

In 2000, Chapman *et al*[29] published that the accepted cost-effective threshold was $50000-$100000 per life-year saved. Rex *et al*[4] considered that the 4 deaths in a worldwide safety review of over 646080 endoscopic procedures using NAAP may have been prevented if an anesthetist had been present. Given the averaged published cost of an anesthetist to deliver sedation in endoscopy ($286)[12], a total of $184778880 would have prevented the loss of 35.08 years. This renders the cost per year of life saved to be $5.3 million. In order to make anesthetist delivered sedation a financially viable practice, Rex *et al*[4] suggest a service cost between $2.70 and $5.40 per case.

CONCLUSION

There is a plethora of data to support the safety profile of propofol in general endoscopy, and many studies that support NAAP. There are also compelling data that support its use in ERCP and EUS. Balanced propofol sedation appears to be an accepted method of delivering high quality sedation with potentially less risk, though propofol monosedation is also safe and effective. With faster recovery times and expedited patient turn over, propofol use also seems to be cost intuitive. Clearly patient selection and appropriate training is a requisite in order to maximise safety. In the world of advanced therapeutic endoscopy, where patient burden, risk, and cost are high, propofol based sedation delivered by non-anesthetic, but appropriately trained individuals, should become the new standard.

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