Issues in Endoscopic Sedation

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Abstract: The subject of endoscopic sedation continues to generate controversy and debate. This article provides a critical analysis of several key issues related to sedation that have recently been the focus of intense interest. Monitored anesthesia care (MAC) is currently the dominant method of endoscopic sedation for approximately one third of all US gastroenterologists. The benefits and cost-effectiveness of this approach remain unclear, as outlined in this article. An alternative to MAC is the administration of propofol by a specially trained nurse or endoscopy assistant, working under the direction of an endoscopist. The scientific merits of the arguments presented by both those in favor of, and those opposed to, this practice are evaluated. In addition, the clinical experience with endoscopist-directed propofol and the challenges associated with its implementation are presented. Other options for endoscopic sedation may soon be available. One approach is computer-assisted delivery of propofol, which is performed by a physician/nurse team. The clinical studies related to this device, along with several other novel methods of sedation, are described.

Keywords
Colonoscopy, endoscopic sedation, fospropofol, propofol, procedural sedation

During the past decade, many gastroenterologists in the United States have adopted new methods of endoscopic sedation. This change in practice has occurred in response to the growing number of patients who expect a painless endoscopic experience, desire on the part of endoscopists to improve practice efficiency, and, in some instances, the payment policies of health insurance companies that provide reimbursement for anesthesia services administered during endoscopy but that are unwilling to compensate an endoscopist who administers comparable sedation to their patient. Monitored anesthesia care (MAC) and endoscopist-directed propofol are the two methods of sedation that have generated the most attention. MAC refers to the service provided by an anesthesia professional to a patient undergoing a diagnostic or

therapeutic procedure, and involves the administration of sedatives, analgesics, or other drugs as necessary to ensure patient comfort. In the majority of cases, patients receiving MAC remain able to protect their airway during the procedure. A recent survey indicated that approximately 33% of endoscopists perform the majority of their procedures using MAC sedation, and this figure is expected to grow by more than 20% annually during the next two years.[1] Those favoring this method indicate that the presence of an anesthesia professional increases the safety, and possibly the effectiveness, of endoscopy. This claim is disputed, however, by those who counter that MAC is not cost-effective in average-risk patients undergoing elective procedures. Similarly, endoscopists and anesthesia specialists are divided with respect to their opinion on endoscopist-directed propofol administration. As expected, those whose self-interests are closely aligned with MAC are also those who are most strongly opposed to the practice. This article critically examines these two methods of endoscopic sedation as well as reviewing the available data on several new and evolving forms of sedation that may help bridge the gap between these divergent opinions.

The Anesthesia Professional Within the Endoscopy Unit

In response to an increase in the demand for endoscopic procedures, endoscopists have focused on strategies that are designed to increase efficiency and throughput in the endoscopy unit. Unquestionably, the most effective strategy has been the use of MAC. The popularity and success of MAC in the United States can be ascribed to three factors: increased patient turnover and throughput, improved patient satisfaction, and, in some instances, reduced operating expenses. A closer examination of these three elements is helpful in order to better understand the phenomenal growth in the utilization of MAC by endoscopists during the past decade.

Compared to sedation using an opioid and benzodiazepine, the effects of propofol on parameters affecting operating efficiency include more rapid induction of sedation, faster recovery, and quicker discharge. Using mathematical modeling to evaluate the effect of a rapid recovery agent on practice efficiency and economics, Vargo and coworkers reported that 3 colonoscopies performed under propofol could be completed in the time required for 2 colonoscopies using midazolam and meperidine.[2] In this analysis, the mean times to discharge with propofol and with midazolam/meperidine were 40.5 minutes and 71.1 minutes, respectively. This analysis did not factor in the additional benefits that could result from reduced delays and lower operating costs in the recovery area. Notwithstanding the benefits associated with fast onset and recovery, it is difficult to distinguish how much of the improved turnover achieved with MAC is the effect of the propofol and how much accrues from the presence of an additional skilled individual who can assist with the preprocedural assessment, preparation of the patient (including placement of the intravenous catheter and monitoring electrodes), intraprocedural monitoring and administration of drugs, and recovery room care. Depending upon the staffing of an endoscopy unit and the division of responsibilities among its members, the availability of an anesthesia professional can improve work efficiency and/or reduce personnel and equipment costs. Finally, it is important to recognize the favorable sedative-hypnotic and amnestic effects of propofol. Most comparative studies have shown that patients prefer sedation with propofol over standard sedation drugs due to the opportunity for painless endoscopy, a very low incidence of postprocedure side effects such as nausea and vomiting, and a rapid return to a clearheaded state upon completion of the procedure.[3]

Unquestionably, the use of MAC increases patient satisfaction and practice efficiency. Although these outcomes are important, the cost-effectiveness of this practice must also be considered. If it can be demonstrated that the presence of an anesthesia specialist improves either the efficacy or safety of endoscopy, an argument could then be made that the additional costs associated with MAC are appropriate. There are no reliable data to support such a claim, however. Well-designed outcome studies comparing the safety and efficacy of MAC versus endoscopist-directed sedation are needed in order to justify the continued expenditure of healthcare resources.

The Controversy over Gastroenterologist-directed Propofol Sedation

The practice of endoscopist-directed propofol administration continues to be a polarizing issue among gastroenterologists and anesthesia specialists.[4,5] Anesthesiologists, the majority of whom oppose this practice, point to the product label as justification for their position, bolstering their argument by indicating that propofol can produce rapid, unpredictable changes in the depth of sedation and noting that propofol lacks a reversal agent.[6] Endoscopists, on the other hand, cite the growing body of published literature and a decade of clinical experience with nurse-directed propofol, both of which support its safety.[7,8] In order to better understand the issues that continue to fuel this debate, it is helpful to examine the arguments and evidence presented by each side.

Propofol, the first of a group of intravenous anesthetic agents known as alkyl phenols, was introduced in the

United States in 1989 for the induction and maintenance of general anesthesia.[9] Its sponsor (Stuart Pharmaceuticals) and the US Food and Drug Administration supported the following wording on its product label: "for general anesthesia or monitored anesthesia care sedation, propofol should be administered only by persons trained in the administration of general anesthesia."[10] Since its introduction into clinical practice 20 years ago, the drug's clinical applications have expanded to include lighter planes of sedation. Currently, more than 70% of propofol sold worldwide is administered for sedation, rather than anesthesia.[11] In spite of extensive evidence demonstrating the safety of propofol use by trained nonanesthesiologists, the warning within propofol's product label regarding anesthesia training remains unchanged. The removal of this cautionary wording from the label would most likely require additional clinical studies and neither AstraZeneca, the manufacturer of propofol injectable emulsion (Diprivan), nor the makers of generic propofol, have demonstrated any interest in sponsoring such studies. Consequently, the major argument of those who oppose the administration of propofol by nonanesthesiologists is based upon an outdated product label that does not reflect the results of recent studies demonstrating the safety of this practice.

Anesthesiologists have put forth two other reasons, in addition to the warnings on the label, in support of their position that propofol usage should remain limited to anesthesia specialists. First, they state that

> propofol is a powerful anesthetic agent that can produce varying levels of sedation along the continuum from sedation to general anesthesia. It is not possible to predict how an individual patient will respond within this continuum. Because of propofol's extremely rapid onset of action and high potency, the desired level of sedation is easily and often exceeded . . . [and] often causes a patient to enter an unintended state of general anesthesia . . .[12]

Unquestionably, propofol is a potent hypnotic agent, but then so too is midazolam. The product label for midazolam contains the following warning:

> Prior to the intravenous administration of midazolam hydrochloride in any dose, the immediate availability of oxygen, resuscitative drugs, age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation should be ensured.[13]

Eighty-six deaths due to oversedation with midazolam were reported during the first 5 years following its approval in 1991.[14] These fatalities resulted from the failure of early investigators to adequately appreciate the dramatic increase in the sedative effect of midazolam with increasing patient age and its synergistic respiratory depressant effect when given in combination with opioids. These miscalculations notwithstanding, improved understanding of its pharmacodynamic properties and changes in the dosing algorithm have since resulted in the safe use of midazolam by endoscopists in millions of patients.

The question remains whether propofol is more dangerous than midazolam. A recent meta-analysis of published studies, performed by the Cochrane collaboration, suggests that the use of midazolam for endoscopic sedation is not associated with more complications than with propofol.[3] This analysis concluded that there was no difference in the risk of either hypoxemia or apnea among endoscopy patients receiving propofol versus those administered traditional sedation. This observation is consistent with several large case series such as a report from Japan reviewing the outcomes of 27,500 endoscopic procedures performed with endoscopist-directed propofol sedation.[15] Twelve patients (0.04%) experienced prolonged apnea, and no patient required any ventilatory intervention other than supplemental oxygen. Similar safety data have been reported by other investigators working in both academic and private practice settings throughout the world. Internationally, more than 450,000 cases with endoscopist-directed propofol have been reported with only 3 mortalities, all occurring in high-risk patients with significant comorbidities.[16] This safety record compares favorably to published mortality rates reported during general anesthesia, MAC, and procedural sedation. There is no evidence to support the contention of some anesthesiologists that patients sedated with propofol by endoscopists "are often being oversedated or are unintentionally entering levels of general anesthesia."[12] In fact, the data demonstrate with convincing clarity that trained endoscopists can safely administer propofol to patients undergoing endoscopy.

Second, anesthesiologists point out that "propofol has no antagonist or reversal medications—in contrast to benzodiazepines and narcotics . . . ."[12] Researchers have considered that the existence of flumazenil and naloxone may make the use of benzodiazepines and opioids inherently safer than propofol.[6] To date, there are no published studies to support this statement. Conversely, the pharmacokinetic properties of these agents provide reason to believe that this conclusion is incorrect. The onset of action and time to peak effect for flumazenil are 2 minutes and 4 minutes, respectively, and the time necessary to reverse sedation is approximately 5 minutes.[17] On the other hand, the half-life of propofol is only 2 minutes.[18,19] It appears likely, therefore, that an oversedated patient receiving propofol would regain responsiveness at least as fast, if not faster, than one who is given flumazenil in order to reverse the effects of midazolam. Nonetheless, a

head-to-head study designed to compare the recovery profiles of these two agents following the induction of deep sedation would be required in order to answer this question.

In addition to safety concerns, the economic impact of MAC should also be considered. The cost of MAC for an endoscopic procedure varies from $150 to several thousand dollars, averaging approximately $400 per case.[20] If each of the 20 million endoscopic procedures performed in the United States were performed with MAC, the cost of anesthesia services annually would be approximately $8 billion. Although it might be reasonable to accept this additional cost if patient safety or procedural outcomes were improved, there is currently no evidence that the use of MAC improves any endoscopic outcome apart from patient satisfaction and throughput. Dr. Orin Guidry, former President of the American Society of Anesthesiology, acknowledged this idea in an open letter to the membership of that professional body.[21] Nevertheless, anesthesiologists continue to insist that the debate over who should sedate our patients should focus on patient safety, not economics. Remarkably, their concern for the "best interests of patients" aligns perfectly with their personal economic interests.

New Directions in Endoscopic Sedation

The rapid growth in the utilization of MAC sedation in certain regions of the United States is a reflection of the desire of many endoscopists to have an improved method of sedation. This desire has been prompted by several factors, including an increased demand for endoscopic services, shrinking reimbursement by payers, and the expectation by a growing number of patients to have a painless endoscopy. In this section, we will review three prospective sedation methods that might fulfill this unmet need.

Fospropofol Disodium

Several prodrug formulations of propofol have been developed in order to circumvent several problems associated with the current formulation of propofol, including the stability of propofol emulsion, complications of lipid infusion, the risk of microbial contamination, and the desire to slow the release of the active drug. Fospropofol disodium (Lusedra injection, MGI Pharma) is the most studied of these prodrugs. Fospropofol (phosphon-O-methyl-2,6-diisopropylpheol) is a water-soluble compound that is rapidly hydrolyzed by alkaline phosphatases to release propofol and several metabolites.[22] Following intravenous administration, fospropofol produces a lower peak plasma propofol concentration than bolus administration of the lipid formulation of propofol. Unlike the lipid emulsion formulation, which produces a rapid spike and fall in propofol concentration, fospropofol is associated with a smooth and predictable rise in propofol. A phase II dose-ranging study showed that an initial bolus dose of 6.5 mg/kg, followed by subsequent bolus doses of 1.6 mg/kg (25% of the initial dose) as needed at 4-minute intervals, led to titratable sedation with an optimum balance of efficacy, safety, and tolerability.[23]

The pivotal phase III study confirmed that fospropofol (6.5 mg/kg) achieved moderate sedation in the vast majority of patients undergoing colonoscopy and was superior to sedation in the low-dose fospropofol group (2 mg/kg).[24] Deep sedation was observed in only 4% of patients in the fospropofol 6.5-mg/kg group (average time, 0.3 minute). Most patients reported being satisfied with their sedation experience. Physicians also reported a high level of satisfaction with fospropofol 6.5 mg/kg. Unfortunately, the US Food and Drug Administration rejected the sponsor's request for a moderate sedation label and instead approved the product with a MAC label, which indicates that the use of this drug will likely be limited to anesthesiologists and certified registered nurse anesthetists, similar to the constraints placed on propofol. The future of this product for procedural sedation in the hands of nonanesthesiologists remains uncertain at the current time.

Computer-assisted Personalized Sedation

The SEDASYS System (Ethicon Endo-Surgery) is a self-contained unit designed to deliver propofol to patients undergoing endoscopy.[25] The system is designed for use by a physician/nurse team and is compliant with existing sedation guidelines. The device consists of two major components: a patient monitoring system and a drug delivery system. The drug delivery unit uses a proprietary software algorithm that enables it to deliver a preselected maintenance dose of propofol (0.25–0.75 μg/kg/min) following the administration of a loading dose (50–100 μg), which is given over a 3-minute period. The system monitors oxygen saturation, heart rate and rhythm, blood pressure, and end-tidal carbon dioxide, as well as patient responsiveness. The responsiveness monitor is a novel device comprised of a hand-held unit and an earpiece that are interconnected through a microprocessor. Physiologic monitors, along with the patient responsiveness unit, provide continuous feedback to the drug infusion system regarding the patient's physiologic condition and level of sedation.[26] The rate of propofol infusion may be adjusted by the microprocessor, based upon feedback from the monitors, in order to maintain the patient at a moderate level of sedation. In addition to the above features, automated oxygen delivery and patient

alarms are integrated into the system in order to provide additional safety mechanisms. For example, the device will respond to oversedation and hypoventilation by stimulating the patient, increasing the oxygen flow rate, and, when appropriate, either reducing or completely interrupting propofol infusion. This approach to sedation has been designated computer-assisted personalized sedation.

The phase III pivotal study was a multicenter, randomized, nonblinded comparative trial that evaluated the SEDASYS system against conventional sedation consisting of a benzodiazepine and an opioid in patients undergoing colonoscopy or esophagogastroduodenoscopy (EGD). A total of 1,000 patients (721 colonoscopy patients, 279 EGD patients) were enrolled at 8 sites throughout the United States.[27] Patients in the SEDASYS arm received a single intravenous bolus of fentanyl, which was followed 3 minutes later by a propofol infusion. The control arm was sedated using midazolam and an opioid according to the investigator's usual sedation protocol. All patients received supplemental oxygen at 2 L/min. The study's primary endpoint was safety, assessed by comparing the duration and depth of hypoxemia (referred to as area-under-the-curve of oxygen desaturation). Additional endpoints included patient and clinician satisfaction measured with newly developed validated instruments, recovery time, and duration of deep sedation. In the colonoscopy cohort, patients in the SEDASYS arm experienced significantly less hypoxemia compared to the patients receiving standard sedation (18 + 125 vs 99 + 510; P=.004). Both patients and clinicians were more satisfied with the sedation provided by the SEDASYS system, compared to that of conventional sedation (93 + 12 vs 91 + 12; P=.052; 92 + 10 vs 76 + 17; P<.001). Recovery time was significantly faster with the SEDASYS system than in patients receiving standard sedation (2.7 + 2.4 min vs 6.3 + 6.8 min; P<.001). More than 99% of all sedation assessments in both treatment groups were considered to be minimal to moderate sedation. Similar findings were observed during EGD. These results suggest that a drug infusion system such as SEDASYS may be a safe and effective option for endoscopic sedation and provide a cost-effective alternative to the current practice of MAC.

Patient-controlled Sedation/Analgesia

This form of drug delivery provides patients with the ability to self-direct the administration of drug when needed or conversely to withhold it. In its simplest form, it may be thought of as personalized drug administration. A handheld device permits the patient to signal the need for the drug by pressing a button. Patient-controlled sedation/analgesia (PCS/A) utilizes a specialized pump that can be programmed to deliver a preset amount of medication. Systems differ in their design, with some offering the option of a continuous infusion mode plus additional doses that are given on demand, whereas other delivery systems are intended to deliver the drug only upon demand. In order for PCS/A to be effective, the drug(s) used in the system must have pharmacokinetic profiles that permit rapid-on and rapid-off effect. Currently, most PCS/A systems that are designed for procedural sedation utilize propofol, either alone or combined with a short-acting opioid such as alfentanil or remifentanil (Ultiva, Bioniche Teoranta).

Several endoscopic studies have compared PCS/A to traditional sedation. Roseveare studied PCS/A with propofol/alfentanil versus conventional sedation in 66 patients undergoing colonoscopy.[28] Patients receiving PCS/A reported slightly more procedure-related pain, though patients in both treatment arms were satisfied with the sedation. As expected, recovery was faster in the PCS/A treatment group. In another study, 100 elderly patients undergoing colonoscopy were randomized to either patient-controlled sedation or intravenous sedation. Both treatment groups were satisfied with their sedation, but patients in the PCS/A group were more likely to describe procedure-related discomfort.[29] Heuss compared propofol administered by bolus versus PCS/A. He observed no differences between the two treatment groups with respect to patient satisfaction or safety parameters.[30] Mandel compared two forms of PCS/A, one using propofol and remifentanil (an ultra-short acting opioid) and the other with midazolam and fentanyl, in 50 patients undergoing colonoscopy.[31] As expected, time to sedation and time to recovery were significantly shorter in the group receiving propofol and remifentanil. Two patients in the propofol arm required intervention by an anesthesiologist.

Conclusion

The practice of MAC will likely continue to generate controversy and debate until outcome studies are available that compare the safety and efficacy of MAC with endoscopist-directed sedation. This will require responsible members of the anesthesia and gastroenterology communities to work together in order to conduct the studies necessary to generate these results. Only then will it be possible to determine with certainty when it is appropriate to use MAC within the endoscopy suite. In the meantime, alternative approaches to endoscopic sedation such as endoscopist-directed propofol, fospropofol, computer-assisted personalized sedation, and PCS/A are being studied to define their respective roles in the endoscopy unit.

References

1. Inadomi JM, Gunnarsson CL, Rizzo JA, Fang H, Ye X. Projected growth rate of anesthesiologist-delivered sedation in colonoscopy and EGD in the United States: 2009-2011. *Gastrointest Endosc*. 2009;69:AB111.
2. Vargo JJ, Bramley TJ, Meyer K, Nightengale B. Practice efficiency and economics. The case for rapid recovery sedation agents for colonoscopy in a screening population. *J Clin Gastroenterol*. 2007;41:591-598.
3. Singh H, Poluha W, Cheung M, Choptain N, Baron KI, Taback SP. Propofol for sedation during colonoscopy. *Cochrane Database Syst Rev*. 2008;(4):CD006268.
4. Rex DK. The science and politics of propofol. *Am J Gastroenterol.* 2004;99:2080-2083.
5. American Society of Anesthesiologists. AANA-ASA Joint Statement Regarding Propofol Administration. Available at: http://www.asahq.org/news/propofolstatement.htm. Accessed March 27, 2009.
6. American Society of Anesthesiologists. Comments Opposing Citizen Petition Requesting Change in Propofol Labeling. Available at: http://www.asahq.org/news/FDAPropofol101905.pdf. Accessed March 27, 2009.
7. Rex DK, Heuss LT, Walker JA, Qi R. Trained registered nurses/endoscopy teams can administer propofol safely for endoscopy. *Gastroenterology.* 2005;129:1384-1391.
8. Cohen LB, DeLegge M, Kochman M, Brill JV, Aisenberg J, et al. AGA institute review on endoscopic sedation. *Gastroenterology*. 2007;133:675-701.
9. Sebel PS, Lowdon JD. Propofol: a new intravenous anesthetic. *Anesthesiology.* 1989;71:260-277.
10. Diprivan injectable emulsion [package insert]. AstraZeneca; 2005.
11. White PF. Propofol: Its role in changing the practice of anesthesia. *Anesthesiology.* 2008;109:1132-1136.
12. Sinclair J. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Available at: http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4192T1.pdf. Accessed March 27, 2009.
13. Midazolam hydrochloride injection [product label]. Accessed March 29, 2009.
14. Arrowsmith JB, Gerstman BB, Fleischer DE, Benjamin SB. Results from the American Society for Gastrointestinal Endoscopy/U.S. Food and Drug Administration collaborative study on complication rates and drug use during gastrointestinal endoscopy. *Gastrointest Endosc*. 1991;37:421-427.
15. Tohda G, Higashi S, Wakahara S, Morikawa M, Sakumoto H, Kane T. Propofol sedation during endoscopic procedures: safe and effective administration by registered nurses supervised by endoscopists. *Endoscopy.* 2006;38:360-367.
16. Deenadayalu VP, Eid EF, Goff JS, Walker JA, Cohen LB, et al. Non-anesthesiologist administered propofol sedation for endoscopic procedures: a worldwide safety review. *Gastrointest Endosc*. 2008;67:AB107.
17. Sage DJ, Close A, Boas RA. Reversal of midazolam sedation with anexate. *Br J Anaesth.* 1987;59:459-464.
18. Amrein R, Hetzel W. Pharmacology of Dormicum (midazolam) and Anexate (flumazenil). *Acta Anaesthesiol Scand Suppl.* 1990;92:6-15.
19. Gross JB, Blouin RT, Zandberg S, Conard P, Jurgen H. Effect of flumazenil on ventilatory drive during sedation with midazolam and alfentanil. *Anesthesiology.* 1996;85:713-720.
20. Aisenberg J, Brill JV, Ladabaum U, Cohen LB. Sedation for gastrointestinal endoscopy: new practices, new economics. *Am J Gastroenterol.* 2005;100:996-1000.
21. Guidry O. Open Letter to ASA Membership. Available at: http://www.asahq.org/Washington/GuidryWeb.pdf. Accessed November 13, 2007.
22. Fechner J, Ihmsen H, Hatterscheid D, Schiessl C, Vornov JJ, et al. Pharmacokinetics and clinical pharmacodynamics of the new propofol prodrug GPI 15715 in volunteers. *Anesthesiology*. 2003;99:303-313.
23. Cohen LB. A randomized, double-blind, dose-response study of fospropofol for moderate sedation during colonoscopy. *Aliment Pharmacol Ther.* 2008;27:597-608.
24. Rex DK, Cohen LB, Kline J, Wang C. Fospropofol disodium is effective and safe for minimal to moderate sedation in patients undergoing colonoscopy: results of a phase 3, randomized, double-blind trial [abstract]. *Gastrointest Endosc.* 2007;65:AB369.
25. Pambianco DJ, McRorie J, Martin J, Politove R, Whitten CJ. Feasibility assessment of computer assisted personalized sedation: a sedation delivery system to administer propofol for gastrointestinal endoscopy. *Gastrointest Endosc.* 2006;63:AB189.
26. Doufas AG, Bakshandeh M, Bjorsten AR, Greif R, Sessler DI. Automated responsiveness test (ART) predicts loss of consciousness and adverse physiologic responses during propofol conscious sedation. *Anesthesiology*. 2001;94:585-592.
27. Pambianco DJ, Pruitt RE, Hardi R, Weinstein ML, Bray WC, et al. Computer-assisted personalized sedation system to administer propofol versus standard of care sedation for colonoscopy and EGD: a 1000 subject randomized, controlled, multi-center, pivotal trial. *Gastroenterology*. 2008;135:294.
28. Roseveare C, Seavell C, Patel P, Criswell J, Kimble J, et al. Patient-controlled sedation and analgesia, using propofol and alfentanil, during colonoscopy: a prospective randomized controlled trial. *Endoscopy.* 1998;30:768-773.
29. Lee DW, Chan AC, Sze TS, Ko CW, Poon CM, et al. Patient-controlled sedation versus intravenous sedation for colonoscopy in elderly patients: a prospective randomized controlled trial. *Gastrointest Endosc*. 2002;56:629-632.
30. Heuss LT, Drewe J, Schnieper P, Tapparelli CB, Pflimlin E, Beglinger C. Patient-controlled versus nurse-administered sedation with propofol during colonoscopy. A prospective randomized trial. *Am J Gastroenterol.* 2004;99:511-518.
31. Mandel JE, Tanner JW, Lichtenstein G, Metz DC, Katzka DA, et al. A randomized, controlled, double-blind trial of patient-controlled sedation with propofol/remifentanil versus midazolam/fentanil for colonoscopy. *Anesth Analg.* 2008;106:434-439.