Endoscopist-Directed Administration of Propofol: A Worldwide Safety Experience

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This article has an accompanying continuing medical education activity on page 1518. Learning Objective: Upon completion of reading this article, successful learners will be able to identify facts about propofol important for its use by non-anesthesiologists.

See CME quiz on page 1518.

BACKGROUND & AIMS: Endoscopist-directed propofol sedation (EDP) remains controversial. We sought to update the safety experience of EDP and estimate the cost of using anesthesia specialists for endoscopic sedation. **METHODS:** We reviewed all published work using EDP. We contacted all endoscopists performing EDP for endoscopy that we were aware of to obtain their safety experience. These complications were available in all patients: endotracheal intubations, permanent neurologic injuries, and death. **RESULTS:** A total of 646,080 (223,656 published and 422,424 unpublished) EDP cases were identified. Endotracheal intubations, permanent neurologic injuries, and deaths were 11, 0, and 4, respectively. Deaths occurred in 2 patients with pancreatic cancer, a severely handicapped patient with mental retardation, and a patient with severe cardiomyopathy. The overall number of cases requiring mask ventilation was 489 (0.1%) of 569,220 cases with data available. For sites specifying mask ventilation risk by procedure type, 185 (0.1%) of 185,245 patients and 20 (0.01%) of 142,863 patients required mask ventilation during their esophagogastroduodenoscopy or colonoscopy, respectively ($P < .001$). The estimated cost per life-year saved to substitute anesthesia specialists in these cases, assuming they would have prevented all deaths, was $5.3 million. **CONCLUSIONS: EDP thus far has a lower mortality rate than that in published data on endoscopist-delivered benzodiazepines and opioids and a comparable rate to that in published data on general anesthesia by anesthesiologists. In the cases described here, use of anesthesia specialists to deliver propofol would have had high costs relative to any potential benefit.**

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The use of propofol for sedation during endoscopic procedures has increased in recent years,[1] because of its favorable pharmacokinetic profile compared with traditional endoscopic sedation with benzodiazepines and

Abbreviations used in this paper: **ASA, American Society of Anesthesiologists; EDP, endoscopist-directed propofol sedation; EGD, esophagogastroduodenoscopy; MAC, monitored anesthesia care.**

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opioids.[2–4] In the United States, propofol is generally administered by anesthesia specialists,[1] despite evidence that endoscopists can administer or supervise the administration of propofol sedation safely without the involvement of an anesthesia specialist.[5–52] The administration of propofol by anesthesia specialists for routine endoscopic procedures is controversial because it adds significantly to the cost of endoscopic procedures[53] without an established improvement in outcomes.[5–52] The administration of propofol by endoscopists or supervision of its administration by endoscopists is controversial because anesthesiologists claim that it is unsafe.[54–56] Concerns about the safety of endoscopist-directed propofol (EDP) have been voiced almost exclusively by the anesthesia community,[54–56] who often cite the warning contained in the package insert that propofol should be given only by persons trained in the administration of general anesthesia.[54,55] The package insert was written before evidence accumulated that nonanesthesiologists could administer propofol safely for endoscopic procedures. Whether EDP is allowed to proceed should be based on evidence about efficacy and safety. A related issue that is relevant to whether endoscopists should sedate their own patients, as has been standard practice in the United States, is whether sedation performed by anesthesia specialists for routine endoscopic cases has acceptable costs compared with other health care practices.

In this report, we describe the safety of EDP for endoscopic procedures, and, on the basis of this safety experience, we estimate the cost of substituting anesthesia specialists for endoscopists in the delivery of sedation for routine endoscopic procedures.

Materials and Methods

Review of Published Cases

The following databases were searched: Ovid MEDLINE and PubMed (1966–November Week 1 2008), EMBASE (1980–2008 Week 45), CINAHL (1982–November Week 1 2008), Cochrane Database of Systematic Reviews (3rd Quarter 2008), and Cochrane Central Register of Controlled Trials (4th Quarter 2008).

The medical subject heading for propofol was combined with all subject headings for medical specialties, specialism, nursing, nursing care, nursing services, nurse's role, health personnel, hospital units, and digestive system endoscopy (or their equivalents in EMBASE and CINAHL). Keyword variants were also added for endoscopist, gastroenterologist, and nonanesthesiologist.

All original studies that used propofol sedation [alone or in combination with other agents(s)] for endoscopic procedures were eligible for inclusion, provided that propofol was administered without the involvement of an anesthesia specialist. We define an anesthesia specialist as either an anesthesiologist or certified registered nurse anesthetist. All of the endoscopists performing endoscopy and administering or directing EDP were gastroenterologists, except for the Australian group (where the endoscopists were gastroenterologists and the anesthetists were primary care physicians) and the Italian group (where the endoscopists were pediatric gastroenterologists and the anesthetists were general pediatric residents). When available, the type of procedure performed [esophagogastroduodenoscopy (EGD), colonoscopy, combined EGD plus colonoscopy, endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography] was documented. We eliminated earlier reports if patients were included in multiple summaries over time,[33–51] or if they concerned non–anesthesiologist-administered propofol with the use of computer-assisted personalized sedation device.[52] If uncertain, we contacted the investigators to make sure no patients were counted twice.

Unpublished Cases

The senior author (D.K.R.) contacted all groups performing EDP that were known to us and invited them to participate in this safety review. These included investigators of previously published studies and abstracts, trainees of 2 teaching programs for EDP in the United States, and all others whom we became aware of through discussion or who contacted us because of awareness of our interest in EDP. All contacted physicians who we reached or who contacted us agreed to submit and did submit their data on safety. Four groups outside the United States with previous publications either could not be reached (n = 2) or had no additional data beyond their most recent publication (n = 1) or the physician had moved to a different country and was no longer using propofol (n = 1). One group in the United States reported to us that they had no additional data since their publication because their program was terminated by the anesthesia group at their institution. However, they confirmed that their patients receiving propofol had no complications. All the participating centers were able to assert that they have kept prospective databases on safety since the inception of their use of propofol except one,[32] which generated its database retrospectively. A total of 28 centers (academic and private practice) contributed unpublished safety data. Seventeen centers were from the United States, 2 were in Japan, and 2 were in Germany. Single centers were in each of the following countries: Switzerland, Australia, Peru, the islands of the Bahamas, Italy, Saudi Arabia, and Canada. Data on endotracheal intubations, neurologic injuries, and deaths were available on all 646,080 endoscopic cases included in the study. Cases listed in both Tables 1 and 2 represent patients rather than procedures; ie, patients undergoing 2 procedures in 1 day are counted as

Table 1. Publications (Papers and Abstracts) From Our Literature Search for Endoscopist-Directed Propofol Sedation

	No. of procedures	No. of mask ventilations	No. of endotracheal intubations	No. of neurologic injuries	No. of deaths
Kulling et al,[6] Switzerland	27,061	6	0	0	0
Vargo et al,[5] United States	38	0	0	0	0
Sipe et al,[25] United States	100	0	0	0	0
Peter et al,[24] Switzerland	5444	0	0	0	0
Tagle et al,[26] Peru	400	0	0	0	0
Tohda et al,[21] Japan	27,500	0	0	0	0
Tohda et al,[22] Japan	120	0	0	0	0
Cohen et al,[12] United States	100	0	0	0	0
Barbi et al,[23] Italy	811	N/A	0	0	0
Vargo et al,[14] United States	5720	0	0	0	0
Cohen et al,[27] United States	819	0	0	0	0
Saenz-Lopez et al,[31] Spain	102	0	0	0	0
Rex et al,[7] United States	36,743	49	0	0	0
Chen et al,[20] China	70	0	0	0	0
Riphaus et al,[19] Germany	75	0	0	0	0
Heuss et al,[13] Switzerland	82,620	157	0	0	0
Wehrmann et al,[28] Germany	99	1	0	0	0
Carlsson and Grattidge,[30] Sweden	45	0	0	0	0
Sinnott et al,[17] United States	1759	0	0	0	0
Yusoff et al,[16] Canada	500	0	0	0	0
Koshy et al,[15] United States	150	0	0	0	0
Wehrmann et al,[29] Germany	80	0	0	0	0
Clarke et al,[8] Australia	22,379	1	0	0	0
Kongkam et al,[9] Thailand	41	0	0	0	0
Gonzalez-Huix et al,[10] Spain	2839	4	0	0	0
Meah and Parikh,[18] United States	254	0	0	0	0
Kulling et al,[11] Switzerland	1391	0	0	0	0
Morse et al,[32] Canada	6396	N/A	0	0	0
Total	223,656	218	0	0	0

N/A, not available.

one case. Neurologic injuries included stroke, transient ischemic attack, and anoxic encephalopathy. The complications were not mutually exclusive, and more than one complication could have occurred in the same patient. We tallied data on mask ventilation by procedure type (EGDs versus colonoscopies), when data were available.

Estimation of the Added Cost of Using Anesthesia Specialists

To estimate the added cost of using anesthesia specialists to administer sedation for all 646,080 cases, we did a simple "back-of-the-envelope" analysis,[57] in which we considered only the direct cost of an anesthesia specialist and assumed the following items. (1) Involvement of an anesthesia specialist would have prevented all 4 deaths without permanent sequelae. (2) Involvement of an anesthesia specialist would not have been associated with fatal complications or permanent sequelae in any of the remaining 646,076 patients. (3) The average cost of an anesthesia specialist to deliver sedation for an endoscopic procedure is $286.[53] (4) The life expectancy of the 70-year-old with widely metastatic cancer was 1 month. The life expectancy of the 68-year-old with mental retardation was 12 years. The life expectancy of the 58-year-old with severe alcoholic cardiomyopathy was 22 years. The life expectancy of the 68-year-old man with pancreatic cancer and hemorrhage was 1 year. (5) We did not attribute lost wages to the cost of EDP, because none of the patients who died was employed. In a simple sensitivity analysis, we further assumed that (1) anesthesia specialists were used only for patients with American Society of Anesthesiologists (ASA) class III or higher, who were estimated to comprise 10% of the study population,[58] and (2) the 4 patients who died would have lived to 85 years.

Statistical Analysis

The incidence of mask ventilation during upper endoscopic versus colonoscopy procedures was compared with the use of the chi-square test.

Results

Of the 28 centers providing previously unpublished cases, all had formal training programs in EDP. Twenty-three centers had didactic training sessions, and 13 required physicians and nurses performing EDP to pass a written test. Twenty-seven centers required trainees to do hands-on supervised administration of propo-

Table 2. Unpublished Data of Safety for Endoscopist-Directed Propofol Sedation[a]

Center	No. of procedures	No. of mask ventilations	No. of endotracheal intubations	No. of neurologic injuries	No. of deaths
1	4080	4	2	0	1
2	7547	1	1	0	0
3	64,152	22	0	0	0
4	14,367	0	0	0	0
5	9068	0	0	0	0
6	12,966	N/A[b]	1	0	1
7	7159	7	0	0	0
8	41,838	59	0	1	0
9	1830	2	0	0	0
10	15,702	6	0	0	0
11	12,721	3	0	0	0
12	21,751	27	2	0	1
13	33,215	1	0	0	0
14	45,007	N/A[b]	0	0	0
15	12,886	2	0	0	0
16	17,450	17	0	0	0
17	690	5	0	0	0
18	26,002	5	0	0	0
19	3667	2	0	0	0
20	3190	89	2	0	1
21	11,680	N/A[b]	0	0	0
22	322	0	0	0	0
23	47,802	3	1	0	0
24	457	0	0	0	0
25	1107	0	0	0	0
26	4277	15	2	0	0
27	891	1	0	0	0
28[c]	600	0	0	0	0
Total	422,424		11	0	4

[a]The position of medical centers here bears no relation to the position of medical centers in Table 1.
[b]N/A, not applicable. Data unavailable.
[c]Data collection was retrospective.

fol, and one used a simulator for training in administration. All centers included training in airway assessment and management, and 5 centers included sessions with an anesthesiologist, sometimes in the operating room. All 28 centers required physicians and nurses to have Advanced Cardiac Life Support certification or an equivalent certification outside the United States. All centers monitored intermittent blood pressure, continuous heart rate, electrocardiography, and pulse oximetry. Two of the 28 centers used capnography routinely. Among the unpublished cases, 4 centers performed systematic telephone follow-up at 30 days on 19,566 cases. Sixteen centers, representing 309,724 cases, had systematic follow-up by telephone call on the working day after the procedure. Eight centers (including 93,134 cases) had follow-up only until discharge from the endoscopy unit on the day of the procedure.

We identified 646,080 (223,656 published and 422,424 unpublished) endoscopic cases performed by nonanesthesiologists using propofol (Tables 1 and 2). There were 11 cases in which endotracheal intubation was performed, and 4 of these patients died. The other 7 patients who underwent endotracheal intubation recovered completely. There were no patients with permanent neurologic sequelae, although one patient had a tonic-clonic seizure, and one had a transient ischemic attack (blindness), both of which resolved without sequelae.

Each of the 4 deaths occurred among the previously unpublished cases and during or after an upper endoscopic procedure. One patient was a 70-year-old man with widely metastatic pancreatic cancer and 2 areas of duodenal obstruction on barium studies. He underwent enteroscopy with fentanyl, midazolam, and propofol, with successful placement of 2 enteral stents. Shortly after completion of the procedure, he became cyanotic. He was mask ventilated and intubated and placed on a ventilator. There was no evidence of aspiration, and his chest x-ray remained clear. However, he required high concentrations of inspired oxygen to maintain adequate oxygen saturation. A pulmonary consultant thought the most likely diagnosis was pulmonary embolism. The family declined investigation or treatment and requested that life support be withdrawn.

A second patient who died was a 68-year-old man with severe mental retardation. He underwent successful percutaneous endoscopic gastrostomy placement with propofol alone. In the recovery area, he awoke from sedation but subsequently developed shortness of breath and hypoxemia for unclear reasons. He was successfully resuscitated and intubated and placed on a ventilator. There was no evidence of aspiration, but his caregiver requested that life support be withdrawn.

A third death occurred in a 58-year-old man with a history of alcoholism, polysubstance abuse, and alcoholic cardiomyopathy. He was on permanent disability. He had previously undergone successful endoscopic dilation of an esophageal stricture with the use of EDP. He was sedated with meperidine, midazolam, and propofol, in anticipation of placement of a removable plastic stent in his esophageal stricture. Shortly after administration of sedation, he suddenly became asystolic, despite oxygen saturation and ventilatory effort that were normal until the moment of collapse. Normal sinus rhythm was restored several times but could not be sustained, and his family requested that the resuscitation effort be stopped. An autopsy showed abnormal levels of several substances that were not revealed to the endoscopy team and severe cardiomyopathy.

The fourth death occurred in a 68-year-old man who presented with hematochezia of 2 days duration and hemoglobin 8.6 g/100 mL. Upper endoscopy with midazolam and propofol showed a large duodenal ulcer with arterial spurting. The patient appeared to aspirate gastric contents, the procedure was stopped, and he was intubated prophylactically. Immediately before intubation

the oxygen saturation was 91%, heart rate was 102, and blood pressure was 95/68 mm Hg. Endoscopy was repeated after intubation, but the bleeding could not be stopped with injection and hemoclip. Emergent surgery showed pancreatic cancer eroding into the duodenal bulb. Ligation of the duodenal artery was unsuccessful, and the patient died 5 days later in hemorrhagic shock.

On the basis of a simple back-of-the-envelope analysis, we estimated that the added cost to use an anesthesia specialist for all 646,080 procedures would be $184,778,880 (646,080 × $286/procedure) and would have prevented loss of 35.08 years of life, such that the cost for each life-year saved is $5.3 million. If used routinely on all patients, irrespective of ASA class, the cost of anesthesia specialist services would have to be between $2.70 and $5.40 to be cost-effective (at $50,000–$100,000 per life-year saved). In sensitivity analyses, under the assumption that all 4 decedents would have lived until age 85 (resulting in 72 life-years saved), the cost per life year saved is $2.6 million. When we further assumed that anesthesia specialists would be used only for ASA III patients (an estimated 10% of all patients),[58] the cost per life-year saved was $527,000. When both assumptions are considered simultaneously (ie, all 4 decedents living to age 85 years and an anesthesia specialist providing assistance for only 10% of all patients) the added cost per life-year saved would be $257,000. Under these conditions, the cost of using an anesthesia specialist would have to cost $56–$111 per procedure to make the cost of each life-year saved between $50,000 and $100,000.

Rates of bag-mask ventilation were available for 569,220 cases. Of these, bag-mask ventilation was reported in 489 cases (0.1%). There were procedure-specific rates of mask ventilation available for 328,108 patients. The mask-ventilation rate was 185 (0.1%) among 185,245 upper endoscopic procedures and 20 (0.01%) of 142,863 during lower endoscopic procedures ($P < .001$, chi-square test). In the remaining patients requiring mask ventilation, the type of procedure was not specified.

No centers used a laryngeal mask airway in any patient. Nasopharyngeal airways were placed in one or more patients at 6 centers (number of patients = 2, 2, 6, 6, and 2 centers did not track the number of placements). There was substantial overlap in patients who had nasopharyngeal tube placement and bag-mask ventilation at these centers. Two centers used oropharyngeal tubes either occasionally (n = 2 patients) or routinely in patients undergoing prolonged procedures.

Discussion

In this report, we summarize published literature and previously unpublished cases about the safety of EDP for endoscopic procedures. Our results indicate that the safety record of propofol administration by endoscopists is superior to the published safety record of opioids and benzodiazepines by endoscopists for gastrointestinal endoscopy.[59–63] Specifically, the overall death rate for EDP that we identified was 1 per 161,515 cases. By comparison, earlier published death rates for nonanesthesiologist administration of opioids and benzodiazepines range from 1 in 1000 to 1 in 11,000,[59–62] and a single report of no deaths in 73,000 cases.[63] A more recent retrospective evaluation of 324,737 cases sedated by endoscopists in the Clinical Outcomes Research Initiative of the American Society for Gastrointestinal Endoscopy, using opioids and benzodiazepines, reported 39 deaths (11 per 100,000), including 28 cardiopulmonary deaths (8 per 100,000).[58] These results for EDP also compare favorably to the published rates of anesthesia-related deaths for general anesthesia. Although some studies have estimated death rates for general anesthesia as low as 1 in 100,000 to 1 in 250,000,[64–69] other more recent studies have estimated anesthesia-related deaths during general anesthesia at 1 in 10,000 to 1 in 50,000.[70–73] A review of a 30-year period found that the incidence of anesthesia-related death has remained unchanged at 1 in 10,000.[74] We were unable to identify published death rates for monitored anesthesia care (MAC), which is generally considered more dangerous than general anesthesia by anesthesia experts.[75]

MAC is unlikely to be cost-effective, even under assumptions that the use of MAC would have prevented the 4 deaths and not caused any other deaths. Using a simple back-of-the-envelope model, we found that the added cost of MAC per life-year saved was more than $5 million, which substantially exceeds the accepted cost-effectiveness threshold of $50,000–$100,000 per life-year saved.[76] This finding, although based on a simple model, was not sensitive to the number of life-years that could have been saved, the proportion of endoscopy requiring use of an anesthesia specialist, or anesthesia cost per procedure.

The current controversy surrounding performance of EDP and the cost of anesthesia specialists for endoscopy is focused on average-risk patients undergoing routine procedures. The deaths in this series occurred in patients and procedures that were neither routine nor average risk. Patient factors almost certainly contributed to the deaths in these patients. Anesthesiologist-administered propofol for truly routine procedures in average-risk patients would be very costly, because we observed no deaths or permanent sequelae among such patients or procedures.

The 4 deaths in this large cohort of patients undergoing EDP occurred in patients with ASA III or higher status, who were undergoing nonroutine medical procedures. Three of the patients had serious underlying illnesses. The results might be interpreted to suggest that such patients should be sedated by anesthesiologists; however, nonanesthesiologists have successfully used propofol for patients with

higher ASA classes,[39] despite the higher risk associated with sedating these patients. In addition, there is no evidence that resuscitation efforts in these patients were delayed or ineffective because of lack of skill on the part of the endoscopist. Thus, conclusions about the appropriateness of EDP in these cases are difficult to draw.

These results confirm previous findings that the risk of complications during EDP is greater during upper endoscopic procedures than during colonoscopy.[7] Indeed, there is still not a single report of death in the literature from EDP for colonoscopy. The reasons why ventilatory support is needed more often during upper endoscopy are unclear. Possible explanations include a deeper average level of sedation, or a higher incidence of coughing and laryngospasm during upper endoscopy with EDP.

Most of the cases described in this report were performed with single-agent propofol; however, propofol can be titrated to moderate sedation when it is given in combination with low doses of opioids or benzodiazepines or both.[8,12] Propofol used in this fashion can result in moderate sedation more reliably than the use of opioids and benzodiazepines alone.[8,12] Furthermore, there are few disadvantages for patient satisfaction or discharge from the endoscopy unit.[44] Anesthesia specialists have stated that combination regimens increase the risk of oversedation and cardiopulmonary complications.[77] This position is incorrect for propofol, because moderate sedation for endoscopy with single-agent propofol is not feasible, although combination therapy is essential to and enables titration of propofol to moderate sedation.[8,12,44] On the basis of this report, both the single-agent model of EDP and combination therapy are safe.

Because there were 4 deaths in this experience, we anticipate that some anesthesia specialists will claim that EDP is unacceptable. This position is inappropriate for several reasons. Deaths occur during sedation by endoscopists using opioids and benzodiazepines,[58–63] during general anesthesia by anesthesiologists,[64–74] and during MAC.[78] Forbidding EDP on the basis of reported deaths is an inconsistent policy because the published safety record of EDP is superior to that of endoscopist-administered opioids and benzodiazepines, the traditional standard of care for endoscopic sedation. MAC performed by anesthesiologists has been associated with a number of deaths and malpractice claims,[78] and one-quarter of claims about MAC-related oversedation by anesthesiologists involved endoscopic procedures.[75,78] EDP is a service that is equivalent in function to MAC. Finally, it is obvious that patient factors contributed to deaths in this experience. Patient factors are an acknowledged cause of deaths associated with anesthesia,[64–73] and in previous studies are often not counted as anesthesia-related deaths.[64–73]

This study had several limitations. First, the reliability of the data depended on self-reporting by the individual participating centers and not all of the centers collected their safety data prospectively (one center collected the data retrospectively). Although this is a potential weakness of our study, we do not believe that it negates our findings because most other case series reporting on sedation or anesthesia risk have also been heavily reliant on self-reporting.[59–74] Second, centers typically did not track late-occurring sedation complications such as pulmonary infections. However, immediate adverse events related to oversedation should have been accurately tracked, because they invariably occur during the procedure or the immediate postprocedure recovery period. Third, the assumptions in our cost calculations could be incorrect. However, we heavily weighted the assumptions to favor anesthesia specialist delivery of propofol. Given that each of the deaths occurred in patients with ASA III or higher status, we could not identify any benefit to offset the cost of using anesthesia specialists for routine endoscopic procedures in ASA class I and II patients. Next, our only end points were death and other safety end points. We did not evaluate potentially important end points of EDP such as patient satisfaction, efficiency, adherence to colorectal cancer screening, adenoma detection, etc. Finally, we are unable to offer conclusions about the ideal method of EDP. Examination of Tables 1 and 2 shows substantial variation between centers in absolute rates of mask ventilation. These differences may reflect use of single-agent propofol compared with combination therapy, different target levels of sedation, differing thresholds of apnea duration before intervention different methods of monitoring of ventilation, and/or different methods or amounts of training before EDP. Although some of these potential explanations have been the subject of previous studies[5,12,13,28,39,41–44,50,51] and each is deserving of investigation, differences in mask ventilation rates do not alter the conclusion that EDP was safe with regard to the critical outcomes of death and permanent sequelae across a range of practices.

In conclusion, EDP is as safe or safer than endoscopist-administered opioids and benzodiazepines, based on the available literature. Further, our findings on the safety of endoscopist-administered sedation show that the use of anesthesiologists for sedation for endoscopic procedures is costly. It is reasonable for health care planners to doubt the wisdom of spending scarce resources on anesthesiologists to assist in endoscopic procedures, particularly those in low-risk patients. Our results support the endorsement of propofol use for endoscopy by trained nonanesthesiologists by organizations in the United States,[3,79] Canada,[80] and Europe.[81] We recommend that all individuals involved in the administration of propofol sedation receive appropriate training before using propofol.[3,79–81]

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. Lichtenstein DR, Jagannath S, Baron TH, et al. Sedation and anesthesia in GI endoscopy. Gastrointest Endosc 2008;68:205–216.
3. American Society for Gastrointestinal Endoscopy. Training guideline for use of propofol in gastrointestinal endoscopy. Gastrointest Endosc 2004;60:167–172.
4. Kazama T, Takeuchi K, Ikeda K, et al. Optimal propofol plasma concentration during upper gastrointestinal endoscopy in young, middle-aged, and elderly patients. Anesthesiology 2000;93:662–669.
5. Vargo JJ, Zuccaro G, Dumot JA, et al. Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial. Gastroenterology 2002;123:8–16.
6. Kulling D, Orlandi M, Inauen W. Propofol sedation during endoscopic procedures: how much staff and monitoring are necessary? Gastrointest Endosc 2007;66:443–449.
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. Clarke A, Chiragakis L, Hillman LC, Kaye GL. Sedation for endoscopy: the safe use of propofol by general practitioner sedationists. Med J Aust 2002;176:158–161.
9. Kongkam P, Pornphisarn B, Rerknimitr R. Non-anesthetist administered propofol for ERCP; efficacy, safety profile and side effect: a prospective randomized trial [abstract]. Gastrointest Endosc 2004;59:AB127.
10. Gonzalez-Huix F, Aldeguer X, Fort E, et al. Sedation without anesthesiologist in 5250 endoscopic procedures: midazolam vs. midazolam + dolantine vs. propofol [abstract]. Gastrointest Endosc 2004;59:AB133.
11. Kulling D, Rothenbuhler R, Inauen W. Safety of nonanesthetist sedation with propofol for outpatient colonoscopy and esophagogastroduodenoscopy. Endoscopy 2003;35:679–682.
12. Cohen LB, Hightower CD, Wood DA, Miller KM, Aisenberg J. Moderate level sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. Gastrointest Endosc 2004;59:795–803.
13. Heuss LT, Froehlich F, Beglinger C. Changing patterns of sedation and monitoring practice during endoscopy: results of a nationwide survey in Switzerland. Endoscopy 2005;37:161–166.
14. Vargo JJ, Holub JL, Faigel DO, Lieberman DA, Eisen GM. Risk factors for cardiopulmonary events during propofol-mediated upper endoscopy and colonoscopy. Aliment Pharmacol Ther 2006;24:955–963.
15. Koshy G, Nair S, Norkus E, et al. Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. Am J Gastrenterol 2000;95:1476–1479.
16. Yusoff IF, Raymond G, Sahai AV. Endoscopist administered propofol for upper-GI EUS is safe and effective: a prospective study in 500 patients. Gastrointest Endosc 2004;60:356–360.
17. Sinnott J, Fricker E, Rogers A. Propofol/meperidine versus midazolam/meperidine: a one year comparison in a community based surgery center. Am J Gastroenterol 2004;99(suppl):S303–S304.
18. Meah N, Parikh PB. Efficacy and safety of nurse-administered propofol as an adjunctive agent of conscious sedation in private non-academic gastroenterology practice setting. Am J Gastroenterol 2004;99(suppl):S313.
19. Riphaus A, Stergiou N, Wehrmann T. Sedation with propofol for routine ERCP in high-risk octogenarians: a randomized, controlled study. Am J Gastroenterol 2005;100:1957–1963.
20. Chen WX, Lin HJ, Zhang WF, et al. Sedation and safety of propofol for therapeutic endoscopic retrograde cholangiopancreatography. Hepatobiliary Pancreat Dis Int 2005;4:437–440.
21. 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.
22. Tohda G, Higashi S, Sakumoto H, Sumiyoshi K, Kane T. Efficacy and safety of nurse-administered propofol sedation during emergency upper endoscopy for gastrointestinal bleeding: a prospective study. Endoscopy 2006;38:684–689.
23. Barbi E, Petaros P, Badina L, et al. Deep sedation with propofol for upper gastrointestinal endoscopy in children, administered by specially trained pediatricians: a prospective case series with emphasis on side effects. Endoscopy 2006;38:368–375.
24. Peter S, Wunderlich P, Beglinger C, Heuss LT. Is nurse administered propofol sedation (NAPS) safe for endoscopies in a gastroenterologist ambulatory practice? [abstract]. Gastroenterology 2007;132:A129.
25. Sipe BW, Scheidler M, Baluyut A, Wright B. A prospective safety study of a low-dose propofol sedation protocol for colonoscopy. Clin Gastroenterol Hepatol 2007;5:563–566.
26. Tagle M, Siu H, Ramos M. Propofol in combination with meperidine and midazolam in colonoscopy and upper endoscopy: first prospective study in private practice in Peru. Rev Gastroenterol Peru 2007;27:367–373.
27. Cohen LB, Dubovsky AN, Aisenberg J, Miller KM. Propofol for endoscopic sedation: a protocol for safe and effective administration by the gastroenterologist. Gastrointest Endosc 2003;58:725–732.
28. Wehrmann T, Grotkamp J, Stergiou N, et al. Electroencephalogram monitoring facilitates sedation with propofol for routine ERCP: a randomized, controlled trial. Gastrointest Endosc 2002;56:817–824.
29. Wehrmann T, Kokabpick S, Lembcke B, et al. Efficacy and safety of intravenous propofol sedation during routine ERCP: a prospective, controlled study. Gastrointest Endosc 1999;49:677–683.
30. Carlsson U, Grattidge P. Sedation for upper gastrointestinal endoscopy: a comparative study of propofol and midazolam. Endoscopy 1995;27:240–243.
31. Saenz-Lopez S, Rodriguez Munoz S, Rodriguez-Alcalde D, et al. Endoscopist controlled administration of propofol: an effective and safe method of sedation in endoscopic procedures. Rev Esp Enferm Dig 2006;98:25–35.
32. Morse JW, Fowler SA, Morse AL. Endoscopist-administered propofol: a retrospective safety study. Can J Gastroenterol 2008;22:617–620.
33. Vargo JJ. Propofol: a gastroenterologist's perspective. Gastrointest Endosc Clin North Am 2004;14:313–323.
34. Sipe BW, Rex DK, Latinovich D, et al. Propofol versus midazolam/meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. Gastrointest Endosc 2002;55:815–825.
35. Ulmer BJ, Hansen JJ, Overley CA, et al. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. Clin Gastroenterol Hepatol 2003;1:425–432.
36. Faulx AL, Vela S, Das A, et al. A changing landscape of practice patterns regarding unsedated endoscopy and propofol use: a national survey [abstract]. Gastrointest Endosc 2004;59:AB131.
37. Dewitt J, Leblanc J, McHenry L, et al. Registered nurse-administered propofol sedation (RNAPS) versus midazolam and meperidine (MM) for endoscopic ultrasound (EUS): a prospective, randomized trial [abstract]. Gastrointest Endosc 2003;57:AB78.

38. Walker J, McIntyre R, Schleinitz P, et al. Nurse-administered propofol sedation without anesthesia specialists in 9152 endoscopic cases in an ambulatory surgery center. Am J Gastroenterol. 2003;98:1744–1750.
39. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Beglinger C. 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.
40. Rex DK, Overley C, Kinser K, et al. Safety of propofol administered by registered nurses with gastroenterologist supervision in 2000 endoscopic cases. Am J Gastroenterol 2002;97:1159–1163.
41. 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.
42. Drake LM, Chen SC, Rex DK. Efficacy of bispectral monitoring as an adjunct to nurse-administered propofol sedation for colonoscopy: a randomized controlled trial. Am J Gastroenterol 2006;101:2003–2007.
43. Fatima H, DeWitt J, LeBlanc J, Sherman S, McGreevy K, Imperiale TF. Nurse-administered propofol sedation for upper endoscopic ultrasonography. Am J Gastroenterol 2008;103:1649–1656.
44. 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.
45. 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.
46. Weston BR, Chadalawada V, Chalasani N, et al. Nurse-administered propofol versus midazolam and meperidine for upper endoscopy in cirrhotic patients. Am J Gastroenterol 2003;98:2440–2447.
47. Chen S, Rex D. Review article: registered nurse administered propofol sedation for endoscopy. Aliment Pharmacol Ther 2004;19:147–155.
48. Rex DK. Review article: moderate sedation for endoscopy: sedation regimens for non-anaesthesiologists. Aliment Pharmacol Ther 2006;24:163–171.
49. Qadeer MA, Vargo JJ, Khandwala F, Lopez R, Zuccaro G. Propofol versus traditional sedative agents for gastrointestinal endoscopy: a meta-analysis. Clin Gastroenterol Hepatol 2005;3:1049–1056.
50. DeWitt JM. Bispectral index monitoring for nurse-administered propofol sedation during upper endoscopic ultrasound: a prospective, randomized controlled trial. Dig Dis Sci 2008;53:2739–2745.
51. Vargo JJ, Zuccaro G Jr, Dumot JA, Shay SS, Conwell DL, Morrow JB. Gastroenterologist-administered propofol for therapeutic upper endoscopy with graphic assessment of respiratory activity: a case series. Gastrointest Endosc 2000;52:250–255.
52. Pambianco DJ, Whitten CJ, Moerman A, Struys MM, Martin JF. An assessment of computer-assisted personalized sedation: a sedation delivery system to administer propofol for gastrointestinal endoscopy. Gastrointest Endosc 2008;68:542–547.
53. Aisenberg J, Brill JV, Ladabaum U, Cohen LB. Sedation for gastrointestinal endoscopy: new practices, new economics. Am J Gastroenterol 2005;100:996–1000.
54. AANA-ASA joint statement regarding propofol administration. Available at: http://www.asahq.org/. Accessed August 15, 2008.
55. ASA House of Delegates statement on safe use of propofol. Available at: http://www.asahq.org/. Accessed August 15, 2008.
56. ASA House of Delegates Statement on granting privileges to nonanesthesiologist practitioners for personally administering deep sedation or supervising deep sedation by individuals who are not anesthesia professionals. Available at: http://www.asahq.org/. Accessed August 15, 2008.
57. Gallivan S. Mathematical methods to assist with hospital operation and planning. Clin Invest Med 2005;28:326–330.
58. Sharma VK, Nguyen CC, Crowell MD, Lieberman DA, de Garmo P, Fleischer DE. A national study of cardiopulmonary unplanned events after GI endoscopy. Gastrointest Endosc 2007;66:27–34.
59. Arrowsmith J, Gerstman BB, Fleischer DE, et al. 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.
60. Daneshmend TK, Bell GD, Logan RF. Sedation for upper gastrointestinal endoscopy: results of a nationwide survey. Gut 1991;32:12–15.
61. Quine MA, Bell GD, McCloy RF, Charlton JE, Devlin HB, Hopkins A. Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing, and sedation methods. Gut 1995;36:462–467.
62. Thompson AM, Wright DJ, Murray W, Ritchie GL, Burton HD, Stonebridge PA. Analysis of 153 deaths after upper gastrointestinal endoscopy: room for improvement? Surg Endosc 2004;18:22–25.
63. Froehlich F, Gonvers J, Fried M. Conscious sedation, clinically relevant complications and monitoring of endoscopy: results of a nationwide survey in Switzerland. Endoscopy 1994;26:231–234.
64. Farrow SC, Fowkes FG, Lunn JN, Robertson IB, Samuel P. Epidemiology in anaesthesia; II: factors affecting mortality in hospital. Br J Anaesth 1982;54:811–817.
65. Eichhorn JH. Prevention of intraoperative anesthesia accidents and related severe injury through safety monitoring. Anesthesiology 1989;70:572–577.
66. Warner MA, Shields SE, Chute CG. Major morbidity and mortality within 1 month of ambulatory surgery and anesthesia. JAMA 1993;270:1437–1441.
67. Spence AA. The lessons of CEPOD. Br J Anaesth 1988;60:753–754.
68. Lunn JN, Devlin HB. Lessons from the confidential enquiry into perioperative deaths in three NHS regions. Lancet 1987;2:1384–1386.
69. Lienhart A, Auroy Y, Pequignot F, et al. Survey of anesthesia-related mortality in France. Anesthesiology 2006;105:1087–1097.
70. Kawashima Y, Takahashi S, Suzuki M, et al. Anesthesia-related mortality and morbidity over a 5-year period in 2,363,038 patients in Japan. Acta Anaesthesiol Scand 2003;47:809–817.
71. Newland MC, Ellis SJ, Lydiatt CA, et al. Anesthetic-related cardiac arrest and its mortality: a report covering 72,959 anesthetics over 10 years from a US teaching hospital. Anesthesiology 2002;97:108–115.
72. Gibbs N, Rodoreda P. Anaesthetic mortality rates in Western Australia 1980–2002. Anaesth Intensive Care 2005;33:616–622.
73. Arbous MS, Grobbee DE, van Kleef JW, et al. Mortality associated with anaesthesia: a qualitative analysis to identify risk factors. Anaesthesia 2001;56:1141–1153.
74. Lagasse RS. Anesthesia safety: model or myth? A review of the published literature and analysis of current original data. Anesthesiology 2002;97:1609–1617.

75. Cohen MM, Duncan PG, Tate RB. Does anesthesia contribute to operative mortality? JAMA 1988;260:2859–2863.
76. Chapman RH, Stone PW, Sandberg EA, Bell C, Neumann PJ. A comprehensive league table of cost-utility ratios and a sub-table of "panel-worthy" studies. Med Decis Making 2000;20:451–467.
77. Lubarsky DA, Candiotti K, Harris E. Understanding modes of moderate sedation during gastrointestinal procedures: a current review of the literature. J Clin Anesth 2007;19:397–404.
78. Bhananker SM, Posner KL, Cheney FW, Caplan RA, Lee LA, Domino KB. Injury and liability associated with monitored anesthesia care: a closed claims analysis. Anesthesiology 2006;104:228–234.
79. Cohen LB, Delegge MH, Aisenberg J, et al. AGA institute review of endoscopic sedation. Gastroenterology 2007;133:675–701.
80. Byrne MF, Chiba N, Singh H, Sadowski DC. Propofol use for sedation during endoscopy in adults: a Canadian Association of Gastroenterology position statement. Can J Gastroenterol 2008;22:457–459.
81. Knape JT, Adriaensen H, van Aken H, et al. Guidelines for sedation and/or analgesia by non-anaesthesiology doctors. Eur J Anaesthesiol 2007;24:563–567.

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Conflicts of interest

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Douglas K. Rex had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.