Dig Dis Sci (2016) 61:1686–1691
DOI 10.1007/s10620-016-4043-3

ORIGINAL ARTICLE

Efficacy and Safety of Propofol-Mediated Sedation for Outpatient Endoscopic Retrograde Cholangiopancreatography (ERCP)

Juliana F. Yang[1] · Priya Farooq[2] · Kate Zwilling[2] · Devi Patel[2] · Ali A. Siddiqui[2]

Received: 10 September 2015 / Accepted: 16 January 2016 / Published online: 29 January 2016

Abstract
Background and Aims Propofol sedation for endoscopy may result in a rapid and unpredictable progression from deep sedation to general anesthesia, leading to potential complications. We investigated the incidence and predictors of sedation-related adverse events (SAEs) in nonintubated patients who underwent outpatient ERCP procedures with propofol sedation.
Methods We conducted a retrospective study of patients who underwent propofol sedation for ERCP procedures. Patients were sedated using propofol in combination with low-dose opiates. Data collected included patient demographics, American Society of Anesthesiologists (ASAs) physical status, and procedure times. SAE includes hypoxia (pulse oximetry <90 %), hypotension (systolic blood pressure <90 mmHg), and conversation to endotracheal intubation. Factors associated with SAEs were examined by univariate analysis and multivariate regression analysis (MVA).
Results A total of 3041 patients were evaluated. The median BMI was 25.2 kg/m^2, and the median ASA score was 3. The mean (±SD) duration of the procedures was 59 ± 23 min. Hypoxia requiring airway manipulation occurred in 28 % ($n = 843$) patients and hypotension requiring vasopressors in 0.4 % ($n = 12$). Forty-nine (1.6 %) patients required endotracheal intubation as a result of food in the stomach. Procedures underwent early termination in 8 (0.3 %) cases due to sedation-related hypotension ($n = 5$) and refractory laryngospasm ($n = 3$). Six patients were admitted after the ERCP for aspiration pneumonia as a result of sedation. Patients who developed SAE were older, had a higher mean BMI, and had longer mean procedure durations. On MVA, older age ($p = 0.003$), female sex ($p = 0.001$), BMI ($p = 0.02$), and ASA class ≥3 ($p = 0.01$) independently predicted SAEs.
Conclusions Propofol can be used safely and effectively as a sedative agent for patients undergoing ERCPs when administered by trained professionals. Age, female sex, BMI, and ASA class ≥3 are independent predictors of SAEs.

Keywords Endoscopic retrograde cholangiopancreatography · Propofol · Adverse events

Introduction

Adequate sedation is a prerequisite in patients who are undergoing a diagnostic or therapeutic endoscopic retrograde cholangiopancreatography (ERCP) [1]. Traditionally, sedation has been achieved using a combination of an opiate and benzodiazepine in order to accomplish a moderate level of sedation (conscious sedation) [2, 3]. Anesthesia-assisted sedation using propofol (2,6-diisopropylphenol) has been increasingly used for advanced endoscopic procedures [4–6].

ERCP is conventionally performed in the prone position which allows for easier passage of scope through the pharynx and allows a comfortable position for the endoscopist [7]. Cote et al. [4] have prospectively demonstrated

✉ Ali A. Siddiqui
Ali.Siddiqui@Jefferson.edu

[1] Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

[2] Division of Gastroenterology and Hepatology, Department of Internal Medicine, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA

the safety of propofol when evaluating 799 patients undergoing ERCP, endoscopic ultrasound, and small bowel enteroscopy. While several studies have demonstrated that ERCP complications when sedated with moderate sedation are similar whether the patient is in prone or supine position, the optimal airway management during ERCP procedures when sedating with propofol is still not well defined [7–9]. The therapeutic spectrum of propofol sedation is narrow and requires careful monitoring since it may induce unintended general anesthesia and apnea. A recent study has demonstrated that the risk of aspiration during colonoscopy is higher in patients receiving anesthesia-assisted sedation compared with those receiving moderate sedation [10]. Due to the aforementioned concerns about the use of propofol sedation for ERCP procedures, the use of general anesthesia is still the sedation of choice in a large number of medical centers [11, 12].

There are limited data on the safety of propofol for therapeutic ERCP procedures performed in prone position. The aim of our retrospective study was to evaluate the safety and sedation-related complications in a large cohort of patients who underwent therapeutic ERCP procedures under propofol sedation, with a specific focus on the number of admission for post-procedure aspiration. In addition, we assessed independent factors that predicted sedation-related adverse events.

Methods

We performed a retrospective analysis of patients who underwent routine diagnostic and therapeutic outpatient ERCP using propofol sedation at a single tertiary care center. These procedures were performed from October 2007 to March 2014. All procedures were performed by three experienced endoscopists who each had performed more than 1000 ERCP examinations. All the authors had access to the study data and had reviewed and approved the final manuscript.

Propofol sedation and monitoring of the patient were performed by a certified registered nurse anesthetist (CRNA) under the direct supervision of a staff anesthesiologist. The anesthesia team in our endoscopy unit consisted of three staff anesthesiologists and six CRNAs who had extensive experience in sedating patients undergoing advanced endoscopic procedures. Induction of sedation was initiated with propofol (0.5–2 mg/kg body weight) alone or combined with a low-dose opioid and/or benzodiazepine. The sedation was then maintained with an injection pump with a starting dose of 80–120 mcg/kg/min and was titrated to maintain deep sedation. All patients received supplemental oxygen via nasal cannula (2–6 L/min) [13]. Cardiovascular parameters were monitored by pulse oximetry and noninvasive blood pressure monitoring.

Patient Data

Patients were identified using electronic medical records and our endoscopy database. We evaluated characteristics including patient demographics, body mass index (kg/m^2), procedure indication, pre-procedure ASA classification, and duration of the procedure (time interval from insertion to final withdrawal of the endoscope). Anesthesia records were accessed to record propofol induction dose (mg/kg), maintenance dose (mcg/kg/min), and total dose (mg). Sedation-related adverse events (SAE) were recorded electronically by the CRNA. This study was approved by the institutional review board of our university.

Patient Monitoring During Procedure

Patient heart rate, oxygen saturation, nasal capnography, and blood pressure were continuously monitored during the procedure by the CRNA. All vitals were recorded at baseline, just before starting sedation, and every 5 min throughout the procedure. If there was any indication of apnea–hypopnea by nasal capnography and clinical observation for more than 10 s, the patient was assessed by the CRNA and airway manipulation (jaw thrust, chin lift, or nasal airway insertion) was performed if needed. If the SpO_2 dropped to <85 % for greater than 30 s despite supplemental oxygen and a jaw thrust, the procedure was stopped until normalization of oxygen saturation was achieved. If the patient was apneic, then he/she was stimulated by noxious stimuli. When this was inadequate, the endoscope was withdrawn and bag-mask assist ventilation was performed, followed by endotracheal intubation if deemed clinically necessary.

Sedation-Related Adverse Outcomes

Sedation-related adverse events (SAE) were defined as hypoxia (pulse oximetry of <90 % anytime during endoscopy) requiring airway manipulation and/or the need to cease the procedure as a result of sedation-related issues [4]. Hypoxia was related to laryngospasm or hypopnea/apnea during the procedure. We also noted the cause and number of patients who required endotracheal intubation during the procedure as per the discretion of the CRNA and attending anesthesiologist. The cause and number of patients who were admitted after the procedure were also evaluated, with a particular emphasis on the patients who developed post-procedure aspiration pneumonia.

Statistical Analysis

All data were given as mean ± SD. The primary outcome of the study was to evaluate the frequency of sedation-related adverse outcomes in our patient cohort. Univariate and multivariate analyses (MVA) on data were performed to determine independent factors that predicted adverse outcomes. Continuous variables were presented as mean ranges and analyzed using a Student's *t* test. Categorical variables were reported as frequencies. Intragroup comparison of performance characteristics was made using the Chi-squared test or Fisher's exact test where appropriate. Statistical significance was determined a priori at $p \leq 0.05$. Analyses were performed using SAS v9.1 (SAS Institute, Cary, NC, USA).

Results

A total of 3041 patients who underwent ERCP using propofol sedation were evaluated over a 72-month period. All patients underwent endoscopy in prone position. Patient characteristics, procedural, and anesthesia pharmacological data are summarized in Table 1. The mean (SD) age of the sample was 58.2 (17.6) years, 46 % were male, and 75.2 % were white. The median BMI was 25.2 (interquartile range 17.2–49.6). It should be noted that 47.3 % of the patients met criteria for ASA class 3 or higher. Combination propofol for induction was used in 62.8 % ($n = 1908$) of cases. The mean case duration ±SD was 59 ± 23 min (range 14–122). The mean total propofol dose was 0.11 ± 0.07 (SD) mg/kg/min.

Overall, airway manipulation due to transient hypoxia ($SpO_2 < 90$ %) was required in 843 (28 %) patients. These included the chin lift/jaw thrust maneuver, bag valve mask ventilation, nasal airway, or mask airway ventilation. Hypotension requiring vasopressors was noted in 12 (0.4 %) patients. Procedures underwent early termination in 8 (0.3 %) cases due to sedation-related hypotension ($n = 5$) and refractory laryngospasm ($n = 3$). Forty-nine (1.6 %) patients were found to have solid food in the stomach at the time of endoscopy and were subsequently converted from propofol sedation to general anesthesia with endotracheal intubation so as to reduce their risk of aspiration pneumonia. Six patients were admitted after the ERCP for aspiration pneumonia as a result of sedation; 4/6 patients had solid food in their stomach.

Table 1 Patient and procedural characteristics

Patient characteristics	
Mean age (years ± SD)	58.2 ± 17.6
Male [sex (%)]	46
Mean BMI (mg/kg^2) ± SD	26.1 ± 5.6
ASA class ≥3 (%)	47.3
Procedural characteristics	
Prone position (%)	100
Mean endoscopy case duration (min) ± SD	59 ± 23
Propofol characteristics	
Combination propofol (%)	62.8
Mean propofol dose (mg/kg/min) ± SD	0.11 ± 0.07

We evaluated the clinical, endoscopic, and pharmacological data to determine predictors of SAEs. On univariate analysis, patients who developed SAE were more likely to be males ($p = 0.001$), older ($p = 0.01$), have a higher BMI ($p = 0.03$), and have a longer mean endoscopy time ($p < 0.01$). The frequencies of patients with SAE were higher in the patients with ASA class 3 or higher (30 vs. 27 %) although this did not reach statistical significance on univariate analysis ($p = 0.29$). The mean total dose of the propofol was similar in patients that with and without SAE (0.1 vs. 0.095 mg/kg/min, respectively, $p = 0.45$).

A multivariate logistic regression analysis was performed to evaluate for independent predictors of SAEs. This analysis was controlled for clinical, procedural, and pharmacological factors. Male sex, older age, a higher BMI, and longer endoscopy time were all independent factors that predicted SAEs (Table 2). Interestingly, ASA class 3 or higher was demonstrated to be an independent predictor of SAEs ($p < 0.01$). Total doses of propofol were not found to be predictor of SAEs.

Discussion

Deep sedation with propofol has been increasingly used for diagnostic and therapeutic endoscopic procedures [14–16]. A recent trial by Cote et al. [4] has demonstrated that propofol can be used safely for advanced endoscopic procedures when administered by a trained professional. However, there are still limited data upon the safety of propofol sedation in patients undergoing an ERCP in prone position [17], as this position can predispose to higher risk of aspiration and vagally mediated hypotension [18, 19]. Our study demonstrates that in a cohort of 3040 patients who underwent ERCP in prone position, propofol sedation was found to be safe and effective without any major complications. Airway manipulation due to transient hypoxemia was required in 28 % patients, and 1.6 % of cases required endotracheal intubation as a result of clinically significant hypoxia. Of the 3040 patients, only six patients (0.2 %) developed aspiration pneumonia. The present trial is the largest study to date evaluating the safety of propofol for ERCP procedures. In addition, it is unique in that all patients were in prone position, with

Table 2 Univariate and multivariate analyses of factors that predict SAEs

Patient characteristics	Sedation-related adverse events (SAE)		Univariate *P* value	Multivariate *P* value
	Yes ($n = 701$)	No ($n = 2340$)		
Age (years, mean ± SD)	61.2 ± 22.6	59.1 ± 21.6	0.02	0.005
Male [sex (%)]	60	53.7	0.001	0.02
BMI (mg/kg^2, mean ± SD)	27.3	26.4	0.004	0.01
ASA class ≥3 (%)	13.9	36.9	0.56	<0.01
Combination propofol (%)	64.9	62.1	0.12	–
Mean propofol dose (mg/kg/min)	0.095	0.101	0.32	–
Case duration (min)	68.8	61.4	<0.01	<0.01

almost half of the patients having an ASA class of 3 or higher and endoscopy times of 59 ± 23 min.

Over the last two decades, ERCP has gradually evolved from being a diagnostic procedure to becoming a complex therapeutic intervention [14]. Therapeutic ERCPs are complex procedures requiring a high level of patient cooperation to facilitate the meticulous interventions performed by the endoscopist; therefore, adequate patient sedation is indispensable.

Sedation options include moderate "conscious" sedation, deep sedation with propofol, and general anesthesia. Moderate sedation is commonly administered using a benzodiazepine/opioid combination and is employed in many endoscopic procedures. However, moderate sedation is often inadequate for therapeutic ERCPs. In one study analyzing over 1000 cases, the ERCP failure rate with conscious sedation was double that with general anesthesia, mainly due to inadequate conscious sedation [12]. In another study, the overall complication rate associated with therapeutic interventions during ERCP was significantly lower in patients under general anesthesia than under conscious sedation [11].

Despite the aforementioned advantages of undergoing ERCP under general anesthesia, there are also limitations. Due to the increased time necessary for patient preparation, induction of anesthesia, tracheal intubation/extubation, and recovery, the required time for each procedure is often prolonged. In addition, the patient may experience nausea and vomiting, sore throat, cardiorespiratory compromise, and delayed return to normal mental function when undergoing ERCP. Despite these limitations, ERCP under general anesthesia is currently the preferred modality in many institutions due to its efficacy.

Deep sedation with propofol is an efficacious alternative used at many centers, including our own. Deep sedation circumvents the prolonged setup time required for general anesthesia, while offering better procedure conditions than conscious sedation. Propofol also has a fast distribution and fast elimination time without a cumulative affect after infusion and is therefore an attractive sedative drug.

Multivariate regression analysis of our 3040 patients undergoing ERCP with deep propofol sedation demonstrated that older age, male sex, increasing BMI, longer case duration, and an ASA class of 3 or higher were independent predictors of developing SAEs. Patients with a higher BMI are obese and hence have a higher incidence of sleep apnea, perhaps accounting for the reason why they are at a higher risk of developing SAEs. Similarly, higher ASA class has been shown as a risk factor for development of hypoxic during EGD and colonoscopy [20]. ASA class 3 or higher was demonstrated to be an independent predictor of SAEs which also suggests that sicker patients are more likely to experience SAEs. These results are in agreement with other studies which evaluated risk factors for airway complications in patients undergoing advanced endoscopic procedures [5, 19, 21]. However, the observation that male sex and older age are risk factors may be a result of underlying comorbidities. These results may help stratify high-risk patients who undergo ERCP, and therefore help decide what type of sedation would be appropriate in this subset of patients.

The present study shows even though 28 % of our patients had SAEs, the majority of these events represented transient hypoxia and hypotension, and these were easily corrected during the procedure. Procedure termination was required only in eight patients. Continuous electronic monitoring of vital signs, oxygen saturation, and blood pressure allowed for careful evaluation of the patient throughout the procedure and maintained their safety. We did not have any fatal cardiopulmonary events reported in our study. These study findings are in concordance with Vargo et al. [22] who reported a 23.7 % incidence of transient hypoxia and hypotension in patients undergoing ERCP with propofol. Overall, results of our and other studies support the conclusion that although SAEs occur during propofol-based sedation during ERCP, they are usually minor and rarely lead to procedure termination or major complications.

Our study demonstrated that 0.2 % patients were admitted to the hospital due to pulmonary aspiration after

ERCP under MAC sedation. A 6-year retrospective study from the Mayo Clinic of 215,488 general anesthetics for elective and emergency surgery between 1985 and 1991 found an incidence of pulmonary aspiration of 1 in 3215 (0.031 %) [15]. Although the percentage of aspiration cases after ERCP with deep sedation is greater than the incidence in general anesthesia cases for surgeries, the value is still low, especially in regard to the high-risk population who are undergoing ERCP.

Our report has several limitations. The data were collected from a single-center, tertiary care referral center where propofol is administered by experienced CRNA's under direct supervision of an anesthesiologist. Propofol has a narrow therapeutic window, and deep sedation may rapidly lead to unintended respiratory suppression requiring airway manipulations (chin lift, jaw thrust, bag-mask assist ventilation) or even tracheal intubation. It is thus of utmost importance that skilled anesthesia personnel trained in airway management be present for administration of propofol for these complex procedures. We also did not compare outcomes of anesthesiologist-administered sedation with those of conscious sedation, although there are many trials to suggest the advantage of propofol-based MAC anesthesia over conscious sedation [14, 22].

In conclusion, propofol-based MAC sedation for ERCP is safe and effective for the majority of patients. Compared to conscious sedation, it provides greater patient comfort, reduced procedure failure rate, and decreased ERCP complications [12]. In contrast to general anesthesia, deep sedation has a lower rate of cardiopulmonary complications and setup time which ultimately reduces cost. Deep sedation with propofol can be safely administered for most ERCPs, with skilled personnel trained in airway management providing the sedation anesthetic. In more complicated patients, general anesthesia should be considered, especially for patients that may be difficult to sedate, for patients that may be difficult to ventilate or intubate, or for patients at high risk of aspiration (i.e., pregnancy, ascites, severe gastroesophageal reflux). General anesthesia may be considered for lengthy and complex ERCP procedures. It is evident that the rate of sedation-related adverse events is low when administered by trained anesthesia personnel, and in light of the increasing trend for gastroenterologist-directed, nurse-administered sedation for advanced procedures, further studies are necessary to determine the clinical training in sedatives and airway management required to safely provide deep sedation with propofol.

Acknowledgments This study was funded entirely through existing intramural funds and salary support.

Author contributions Juliana F. Yang, MD, Priya Farooq, MD, and Devi Patel, MD, contributed to analysis and interpretation of the data; drafting of the article; and final approval of the article. Ali A. Siddiqui, MD, contributed to conception and design; analysis and interpretation of the data; drafting of the article; and final approval of the article. Kate Zwilling, BSN, analyzed and interpreted the data and finally approved the article.

Compliance with ethical standards

Conflict of interest The authors attest that they have no commercial associations (e.g., equity ownership or interest, consultancy, patent and licensing agreement, or institutional and corporate associations) that might be a conflict of interest in relation to the submitted manuscript. None of the authors have any potential personal—in addition to financial—conflicts of interest.

References

1. Jowell PS, Eisen G, Onken J, Bute BP, Ginsberg B. Patient-controlled analgesia for conscious sedation during endoscopic retrograde cholangiopancreatography: a randomized controlled trial. *Gastrointest Endosc*. 1996;43:490–494.
2. Cohen LB, Delegge MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. *Gastroenterology*. 2007;133:675–701.
3. McCloy R, Nagengast F, Fried M, Rohde H, Froehlich F, Whitwam J. Conscious sedation for endoscopy. *Eur J Gastroenterol Hepatol*. 1996;8:1233–1240.
4. Cote GA, Hovis RM, Ansstas MA, et al. Incidence of sedation-related complications with propofol use during advanced endoscopic procedures. *Clin Gastroenterol Hepatol*. 2010;8:137–142.
5. Wani S, Azar R, Hovis CE, et al. Obesity as a risk factor for sedation-related complications during propofol-mediated sedation for advanced endoscopic procedures. *Gastrointest Endosc*. 2011;74:1238–1247.
6. Jung M, Hofmann C, Kiesslich R, Brackertz A. Improved sedation in diagnostic and therapeutic ERCP: propofol is an alternative to midazolam. *Endoscopy*. 2000;32:233–238.
7. Tringali A, Mutignani M, Milano A, Perri V, Costamagna G. No difference between supine and prone position for ERCP in conscious sedated patients: a prospective randomized study. *Endoscopy*. 2008;40:93–97.
8. Terruzzi V, Radaelli F, Meucci G, Minoli G. Is the supine position as safe and effective as the prone position for endoscopic retrograde cholangiopancreatography? A prospective randomized study. *Endoscopy*. 2005;37:1211–1214.
9. Ferreira LE, Baron TH. Comparison of safety and efficacy of ERCP performed with the patient in supine and prone positions. *Gastrointest Endosc*. 2008;67:1037–1043.
10. Cooper GS, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. *JAMA Intern Med*. 2013;173:551–556.
11. Etzkorn KP, Diab F, Brown RD, et al. Endoscopic retrograde cholangiopancreatography under general anesthesia: indications and results. *Gastrointest Endosc*. 1998;47:363–367.
12. Raymondos K, Panning B, Bachem I, Manns MP, Piepenbrock S, Meier PN. Evaluation of endoscopic retrograde cholangiopancreatography under conscious sedation and general anesthesia. *Endoscopy*. 2002;34:721–726.
13. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology*. 2002;96:1004–1017.
14. 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.

15. Triantafillidis JK, Merikas E, Nikolakis D, Papalois AE. Sedation in gastrointestinal endoscopy: current issues. *World J Gastroenterol*. 2013;19:463–481.
16. Horiuchi A, Nakayama Y, Hidaka N, Ichise Y, Kajiyama M, Tanaka N. Low-dose propofol sedation for diagnostic esophagogastroduodenoscopy: results in 10,662 adults. *Am J Gastroenterol*. 2009;104:1650–1655.
17. Paspatis GA, Manolaraki MM, Vardas E, Theodoropoulou A, Chlouverakis G. Deep sedation for endoscopic retrograde cholangiopancreatography: intravenous propofol alone versus intravenous propofol with oral midazolam premedication. *Endoscopy*. 2008;40:308–313.
18. Chainaki IG, Manolaraki MM, Paspatis GA. Deep sedation for endoscopic retrograde cholangiopacreatography. *World J Gastrointest Endosc*. 2011;3:34–39.
19. Berzin TM, Sanaka S, Barnett SR, et al. A prospective assessment of sedation-related adverse events and patient and endoscopist satisfaction in ERCP with anesthesiologist-administered sedation. *Gastrointest Endosc*. 2011;73:710–717.
20. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Beglinger C. Safety of propofol for conscious sedation during endoscopic procedures in high-risk patients—a prospective, controlled study. *Am J Gastroenterol*. 2003;98:1751–1757.
21. Wehrmann T, Riphaus A. Sedation with propofol for interventional endoscopic procedures: a risk factor analysis. *Scand J Gastroenterol*. 2008;43:368–374.
22. Vargo JJ, Zuccaro G Jr, Dumot JA, et al. Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial. *Gastroenterology*. 2002;123:8–16.