Sedation during upper GI endoscopy in cirrhotic outpatients: a randomized, controlled trial comparing propofol and fentanyl with midazolam and fentanyl

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Background: Patients with liver cirrhosis frequently undergo diagnostic or therapeutic upper GI endoscopy (UGIE), and the liver disease might impair the metabolism of drugs usually administered for sedation.

Objective and Setting: To compare sedation with a combination of propofol plus fentanyl and midazolam plus fentanyl in cirrhotic outpatients undergoing UGIE.

Design: A prospective, randomized, controlled trial was conducted between February 2008 and February 2009.

Main Outcomes Measurements: Efficacy (proportion of complete procedures using the initial proposed sedation scheme), safety (occurrence of sedation-related complications), and recovery time were measured.

Results: Two hundred ten cirrhotic patients referred for UGIE were randomized to 2 groups: midazolam group (0.05 mg/kg plus fentanyl 50 μg intravenously) or propofol group (0.25 mg/kg plus fentanyl 50 μg intravenously). There were no differences between groups regarding age, sex, weight, etiology of cirrhosis, and Child-Pugh or American Society of Anesthesiologists classification. Sedation with propofol was more efficacious (100% vs 88.2%; $P < .001$) and had a shorter recovery time than sedation with midazolam (16.23 $\pm$ 6.84 minutes and 27.40 $\pm$ 17.19 minutes, respectively; $P < .001$). Complication rates were similar in both groups (14% vs 7.3%; $P = .172$).

Limitations: Single-blind study; sample size.

Conclusion: Both sedation schemes were safe in this setting. Sedation with propofol plus fentanyl was more efficacious with a shorter recovery time compared with midazolam plus fentanyl. Therefore, the former scheme is an alternative when sedating cirrhotic patients undergoing UGIE. (Gastrointest Endosc 2011;73:45-51.)

Cirrhotic patients often undergo upper GI endoscopy (UGIE) for the screening or treatment of complications related to portal hypertension. These endoscopic procedures can cause pain or discomfort, and sedation is recommended to minimize anxiety and provide conditions to perform the examination safely.[1] It also increases willingness to undergo a repeat procedure.[2] Benzodiazepines alone or in combination with opioids are still the most commonly used drugs for sedation in general patients during UGIE.[1,3,4] Midazolam is preferred over diazepam because of its shorter induction and recovery times and marked amnesic properties.[1,4] Midazolam administration by nonanesthesiologists is largely accepted, and there is an available antagonist (flumazenil). However, the half-life is prolonged in the presence of obesity, renal or liver failure, and advanced age, which may increase the risks of adverse effects in such patients.[4] Midazolam use can trigger encephalopathy in cirrhotic patients.[5]

Propofol is a hypnotic agent that can be safely used for moderate or deep sedation during endoscopic procedures.[6-8]

Abbreviations: ASA, American Society of Anesthesiologists; OAAS, Observer's Assessment of Alertness/Sedation Scale; UGIE, upper GI endoscopy.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2010.09.025

Received May 31, 2010. Accepted September 14, 2010.

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Propofol does not need dose adjustment in liver cirrhosis and offers many advantages over midazolam because of its faster onset of action, shorter effect, and faster recovery of motor and cognitive functions.[9] Previous studies showed that propofol did not cause encephalopathy in cirrhotic patients.[10,11]

There are no specific sedation guidelines for cirrhotic patients. Liver cirrhosis impairs protein synthesis, alters drug metabolism pathways, and compromises hepatic blood flow. All of these factors may affect the pharmacokinetics of sedative drugs.[9] Considering this, we designed a prospective study with cirrhotic outpatients to compare efficacy, safety, and recovery time during UGIE with 2 sedation schemes: midazolam plus fentanyl and propofol plus fentanyl.

Take-home Message

- Patients with cirrhosis are more susceptible to complications related to sedation than the general population, and there is no consensus about sedation during endoscopic procedures for these patients. Propofol and fentanyl are an alternative to midazolam and fentanyl for these patients during diagnostic or therapeutic upper GI endoscopy.

PATIENTS AND METHODS

A single-blind, prospective, randomized, controlled trial was conducted from February 2008 to February 2009 in Hospital São Paulo of Universidade Federal de São Paulo, Brazil. All patients provided written informed consent before enrollment. This study received previous approval from our institution's ethics committee.

The following outcomes were analyzed:

- Efficacy: the proportion of complete procedures performed by using the initial proposed sedation scheme. The sedation scheme was considered ineffective when the procedure was interrupted by agitation or intolerance by the patient despite the maximum sedative dose. In this case, sedation was conducted by an examiner according to the endoscopist's personal preference.
- Safety: frequencies of the following complications during procedure or recovery time:
  a. Hypoxemia: This was defined as oxygen saturation less than 90% and patient unresponsive for 15 seconds to jaw extension maneuver, verbal stimulus, or an increase in oxygen supplementation. This was considered serious when mask ventilation or orotracheal intubation was necessary.
  b. Hypotension: This was defined as a 20% decrease in mean blood pressure or systolic pressure less than 90 mm Hg and/or diastolic pressure less than 50 mm Hg. It was considered serious when vasoactive drugs or saline solution infusion was necessary.
  c. Bradycardia: This was defined as a 25% decrease in initial heart rate or heart rate less than 55 beats per minute. It was considered a serious complication when inotropic drugs were necessary or cardiac arrest occurred.

  Antagonists of midazolam and fentanyl were used when serious complications occurred or in situations in which mild complications did not respond to the procedures described.
- Recovery time: This was defined as the time between the end of the procedure and hospital discharge.

Patients

Outpatients between 18 and 75 years old with liver cirrhosis (diagnosed by physical examination, biochemical tests, imaging studies, and histological evidence), classified by Child-Pugh classification in A, B, or C and who were referred to diagnostic or therapeutic UGIE were included for analysis. We excluded all patients with emergency procedures; contraindications to midazolam, propofol, or fentanyl administration; American Society of Anesthesiologists (ASA) classification IV or V; continued use of alcohol; illicit drugs or drugs that act in the central nervous system such as benzodiazepines, narcotics, and or neuroleptics within the past month; clinically detectable hepatic encephalopathy; hypotension (systolic blood pressure <90 mm Hg and/or diastolic <50 mm Hg); or bradycardia (heart rate <55 beats per minute).

Clinical procedure and interventions

All endoscopic procedures were performed with the standard technique. The duration of the procedure was defined as the time elapsed between the passage of the endoscope through the cricopharyngeus muscle until its removal.

Randomization was performed by an independent physician by sequentially opening numbered opaque envelopes with group allocation cards in a random sequence. Patients were randomized in 2 groups: (1) midazolam group: midazolam 0.05 mg/kg with additional doses of 1 mg every 2 minutes when necessary until the maximum dose (0.1 mg/kg or 10 mg) plus fentanyl 50 μg in a single dose administered intravenously and (2) propofol group: propofol 0.25 mg/kg with additional doses of 20 to 30 mg every 30 to 60 seconds when necessary until the maximum dose (400 mg) plus fentanyl 50 μg in a single dose administered intravenously.

Fentanyl was added to propofol and midazolam because of its analgesic properties. In the procedure room, there was a nurse and 2 gastroenterologists who were not blinded to sedation drugs. Sedation in both groups was administered by a dedicated gastroenterologist, and moderate sedation was the objective (defined by the Observer's Assessment of Alertness/Sedation Scale [OAAS] as lev-

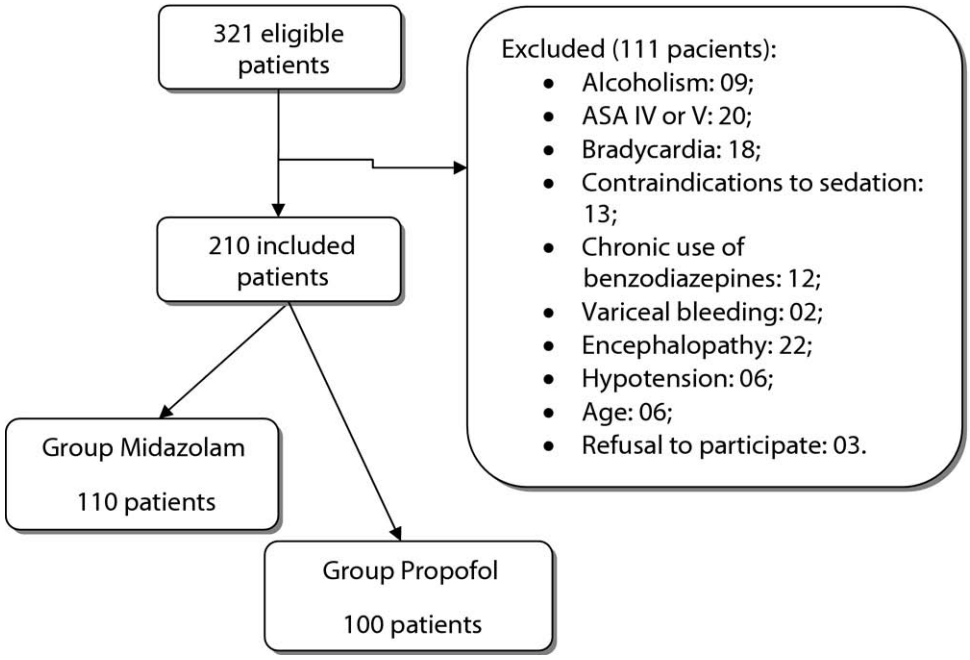

Figure 1. Patient flow during the study.

els of ≥3[12]) (see Online Appendix, available online at www.giejournal.org). Patients were blinded to randomization.

All patients were monitored with pulse oximetry and noninvasive blood pressure measurement. During the procedure, heart rate, respiratory frequency, oxygen saturation, blood pressure, and level of consciousness (OAAS) were measured and recorded every 5 minutes. In the recovery room, a third gastroenterologist, blinded to the sedation scheme, measured and recorded the same parameters every 10 minutes until hospital discharge. All patients received 3 L/min oxygen supplementation by nasal catheter during the endoscopic examination and in the recovery room when necessary.

Vital signs within 20% of baseline, oxygen saturation greater than 92% in room air, the ability to stand up without assistance, and 2 measurements of 5 on the OAAS were necessary before patients were discharged.

The study was interrupted, and statistical analysis was performed 1 year after the start of inclusion or when the number of patients was estimated to be reached, whichever came first.

Statistical analysis

Sample size was calculated by using comparison of proportions test, considering a level of significance of .05, power of 0.7, and expected efficacy of 97% in the propofol group and 87% in the midazolam group. This resulted in a sample size of 110 patients in each group. At our institution, we historically observed an 85% to 90% efficacy rate for sedation in these patients using midazolam and fentanyl. We therefore chose 87% efficacy as our assumption for the purposes of determining sample size.

Parametric data were presented as means ± standard deviation and were analyzed by using Student *t* test. Nonparametric data were presented as medians (ranges), and the Mann-Whitney test was used for analysis. Qualitative variables were expressed as frequencies and percentages, and proportions were compared by using χ^2 tests with continuity correction or the Fisher exact test when appropriate. We adopted a level of significance of .05. All data analyses were performed by using SPSS for Windows, version 16.0 (SPSS Inc, New York, NY).

RESULTS

A total of 321 consecutive cirrhotic outpatients were analyzed for inclusion; 111 patients were excluded according to previously described criteria. Two hundred ten patients were randomized, 110 in the midazolam group and 100 in the propofol group (Fig. 1). Inclusion was interrupted after 1 year of study according to the criteria defined because statistical significance was reached before the number of patients previously estimated.

There were no significant statistical differences between the groups regarding age, sex, weight, cirrhosis etiology, and ASA or Child-Pugh classification (Table 1). Diagnostic UGIE was the most common endoscopic procedure, accounting for 75 of 110 patients (68.2%) in the midazolam group and 61 of 100 patients (61%) in the propofol group ($P = .489$). The procedures, their duration, and the mean administered dose in both groups are listed in Table 2.

TABLE 1. Demographic characteristics of groups

Characteristics	Midazolam group (n = 110)	Propofol group (n = 100)	*P* value
Mean (SD) age, y	52.57 (11.51)	54.12 (10.51)	.312*
Male, no. (%)	84 (76.4)	64 (64)	.070†
Mean weight (kg)	69.00 (61.75-80.00)	71.00 (60.25–84.75)	.966‡
Etiology, no. (%)			.085†
Virus	57 (51.8)	52 (52)	
Alcohol	32 (29.1)	17 (17)	
Virus + alcohol	7 (6.4)	8 (8)	
Other	14 (12.7)	23 (23)	
ASA, no. (%)			.176†
2	84 (76.4)	67 (67)	
3	26 (23.6)	33 (33)	
Child-Pugh, no. (%)			.552†
A	82 (74.5)	70 (70)	
B	23 (20.9)	22 (22)	
C	5 (4.5)	8 (8)	

SD, Standard deviation; *ASA*, American Society of Anesthesiologists.
*Chi-square test.
†Student *t* test.
‡Mann-Whitney test.

The OAAS scores before procedures and at discharge were the same in both groups (all patients had a score of 5). During the procedure, 20 patients (5 in the propofol group and 15 in the midazolam group) had scores lower than intended, without statistically significant differences ($P = .104$). Most patients (95% in the propofol group and 86.4% in the midazolam group) presented levels equal to or greater than 3, as expected.

All of the patients in the propofol group had a complete examination with initially proposed sedation scheme. In the midazolam group, 13 of 110 procedures (11.8%) could not be performed even with maximum doses of midazolam ($P < .001$). All of these patients became agitated or did not tolerate the procedure despite sedation. Endoscopic examinations in these cases were completed after the administration of low doses of propofol.

In the midazolam group, there were no differences regarding mean age ($P = .800$), sex ($P = .249$), mean weight ($P = .882$), cirrhosis etiology ($P = .881$), Child-Pugh ($P = .459$), or ASA classifications ($P = .678$) between the subgroups with effective or ineffective sedation. Variceal band ligation was the most frequent procedure, performed in 10 of 13 patients in whom sedation was inefficacious ($P = .001$). The mean dose of midazolam, in milligrams, was higher in the group with inefficacious sedation (7.30 ± 1.52 vs 4.57 ± 1.34; $P < .001$).

Complications were not statistically different between the groups and were observed in 22 of 210 patients (10.5%). Procedure discontinuation was not necessary in any cases (Table 3). In the midazolam group, 8 of 110 patients (7.3%) experienced complications compared with 14 of 100 (14%) in the propofol group ($P = .112$). In the propofol group, 2 simultaneous complications were detected in 1 patient, mild hypotension and bradycardia, without clinical repercussions.

Serious complications occurred in 5 of 210 patients (2.4%) (hypotension that required saline solution infusion only). Four were recorded in the midazolam group and 1 in the propofol group. Only 1 patient in the midazolam group received flumazenil because of partial response to saline solution infusion. This patient was classified as Child-Pugh C/ASA III and underwent variceal band ligation.

The mean recovery time (in minutes) in the midazolam group and the propofol group was, median (percentiles), 20.50 (range, 12.50-35.00) and 15.00 (range, 10.00-20.00), respectively ($P < .001$).

TABLE 2. Endoscopic procedure type, duration, and mean doses of sedatives administered in groups

	Midazolam group (n = 110)	Propofol group (n = 100)	*P* value
Procedure type			.489*
Diagnostic (%)	75/110 (68.2)	61/100 (61)	
Band ligation (%)	31/110 (28.2)	33/100 (33)	
Sclerosis (%)	4/110 (3.6)	6/100 (6)	
Mean sedation doses, mg/kg			
Diagnostic (SD)	0.061 (0.018)	1.059 (0.444)	
Band ligation (SD)	0.084 (0.015)	1.998 (1.208)	
Sclerosis (SD)	0.071 (0.024)	1.556 (0.412)	
Procedure duration, min (median with percentiles)			
Diagnostic	5.00 (4.00– 6.00)	4.00 (3.00–5.00)	.210†
Band ligation	14.00 (10.00–17.50)	12.00 (10.00–15.50)	.725†
Sclerosis	12.50 (8.50–17.25)	10.00 (8.25–17.50)	.831†

SD, Standard deviation.
*Chi-square test.
†Mann-Whitney test.

TABLE 3. Complications rate

Complications (%)	Midazolam group (n = 110)	Propofol group (n = 100)	*P* value
Total	7.3 (8/110)	14 (14/100)	.112*
Hypoxemia			.606†
Mild	0.9 (1/110)	2 (2/100)	
Severe/apnea/invasive ventilation	—	—	
Hypotension			>.999*
Mild	2.7 (3/110)	6 (6/100)	
Severe	3.6 (4/110)	1 (1/100)	
Bradycardia			.550†
Mild	0.9 (1/110)	6 (6/100)	
Severe	—	—	

*Chi-square test.
†Fisher exact test.

DISCUSSION

UGIE is the method of choice for the diagnosis and treatment of esophageal and gastric varices.[13] Sedation is part of endoscopic procedures and is administered mostly by gastroenterologists. In the United States, as many as 98% of gastroenterologists administer sedation during UGIE.[14] In a recent meta-analysis, sedation was associated with increased patient satisfaction and greater willingness to repeat the procedure.[2] However, most sedation drugs depend on hepatic metabolism, and because of impaired liver function, sedation represents a risk factor for complications in cirrhotic patients.

We performed a single-blind, prospective, randomized trial to assess the efficacy, safety, and recovery time during diagnostic or therapeutic UGIE in cirrhotic outpatients in 2 groups: midazolam and fentanyl and propofol and fentanyl.

During the study, 210 cirrhotic outpatients were randomized to 1 of 2 groups. Chronic viral hepatitis and alcoholism were the most common etiologies of cirrhosis in this study. ASA II and Child-Pugh A patients were the most common, suggesting that outpatients have better liver function and less severe comorbidities. Patients who were ASA IV or V were excluded because they have a higher risk of complications, and assistance of an anesthesiologist during sedation for these patients is recommended.

The groups were homogeneous in terms of demographics. Age and weight were similar in both groups. These characteristics may interfere with the dose and change the risks of complications. Younger and thin patients present higher anxiety levels and may need higher doses.[15]

Diagnostic UGIE was the most common procedure. However, more than 30% of endoscopic procedures performed in the 2 groups were therapeutic for esophageal varices. Variceal band ligation or sclerotherapy of varices needs adequate sedation for completion. In both situations, patients should be reassessed endoscopically. Furthermore, 80% of patients have submitted to previous UGIE. This reinforces the need to study safety and efficacy sedation schemes in these patients.

There are no guidelines for sedation in cirrhotic patients, and there are few studies assessing sedation in cirrhotic patients during UGIE.[5,9,11,16-19] Nevertheless, caution is advised when sedation with benzodiazepines and opioids is administered in patients with liver disease. Hepatic flow is one of the main factors involved in metabolism and elimination of midazolam.[20] The release of benzodiazepines and the bind protein synthesis is unclear in cirrhotic patients.[20-22] Benzodiazepine receptors may increase in cirrhotic patients, which increases sensitivity to these drugs, making patients more susceptible to complications.[18,20]

The propofol with fentanyl scheme was more efficacious than the scheme with midazolam. Midazolam sedation scheme failed in 13 of 100 patients (11.8%) because of agitation. Paradoxical reactions with benzodiazepines are seen in less than 1% of patients. They are usually idiosyncratic reactions but may be related to alcohol abuse or psychiatric disorders.[23] However, there were no statistical differences between these 13 patients and the remaining midazolam group when considering the etiology of cirrhosis. One shortcoming of this study might have been that doses of midazolam were lower than doses used in previous studies.[16,17] Nevertheless, the average dose observed in the group whose sedation was considered ineffective is consistent with the average weight observed for this group, which means that the maximum dose was achieved but without the expected results.

Patient satisfaction with propofol sedation for endoscopic procedures is equivalent or superior to that of standard sedation. Propofol administration during ERCP and EUS is more cost-effective than standard sedation.[2,7,24-26] Propofol has a favorable pharmacokinetic profile with a short half-life and rapid elimination.[1,4,20] Dose adjustment is not necessary in cirrhosis, and propofol metabolism is not impaired in this clinical situation.[1,20] Therefore, propofol is an alternative for sedation in patients with liver disease. In a prospective, randomized study, Weston et al[16] demonstrated in cirrhotic patients that propofol was more efficacious and well tolerated compared with midazolam plus meperidine. They included only ASA I or II patients for diagnostic procedures, and sedation was administered by a nurse. The mean doses of propofol and midazolam were higher than in our study. Although not statistically significant, higher levels of satisfaction were obtained with propofol. We did not assess patient satisfaction in this study.

Benzodiazepines may also precipitate the probable worsening of hepatic encephalopathy. Assy et al,[5] in a case-control study, demonstrated that most cirrhotic patients with subclinical encephalopathy before sedation became worse after benzodiazepine administration. Vasudevan et al[18] observed that 54.1% of cirrhotic patients presented prolonged number connection test times, suggesting subclinical encephalopathy before UGIE, and 75.4% had impaired test results after sedation with benzodiazepines.

Propofol does not trigger acute deterioration of minimal encephalopathy.[11,17] In a cohort study, Amorós et al[11] demonstrated that deep sedation with propofol did not precipitate minimal or overt hepatic encephalopathy. This observation was confirmed by Riphaus et al[17] in a prospective, randomized study comparing propofol with midazolam for sedation in cirrhotic patients during therapeutic endoscopic procedures. In this study, no serious complications were recorded, and the authors recommended that propofol should be an alternative to midazolam in cirrhotic patients. We did not evaluate hepatic encephalopathy.

Because of impaired drug metabolism in cirrhotic patients, some authors have proposed diagnostic UGIE without sedation with thin endoscopes in these patients.[27,28] However, discomfort, pain, and anxiety related to the procedure may reduce the acceptability.[29] In our study, sedation was administered by a gastroenterologist. Many studies demonstrate that administration of sedation by nonanesthesiologists, nurses, or physicians is safe as long as adequate monitoring and knowledge of drug pharmacology and metabolism are provided.[7,24,26,30,31] The risk of propofol-related complications has been associated with deep sedation.[32] However, Qadeer et al[33] observed deep sedation in as many as 26% of patients sedated with benzodiazepines even when moderate sedation was intended. In another study, Patel et al[34] detected deep sedation in as many as 80% of patients who underwent elective examinations with midazolam plus meperidine. In our study, 15 patients in the midazolam group had deeper levels of sedation according to the OAAS score. However, there

were no statistically significant differences compared with the propofol group. In a recent publication, in more than 646,000 endoscopic procedures, propofol administration by nonanesthesiologists had a lower mortality rate than with conventional sedation with benzodiazepines and opioids.[30]

Sedation with propofol leads to a shorter recovery time. A shorter recovery time benefits the patient by allowing a faster return to daily activities. For the endoscopy unit, the shorter recovery time improves patient flow and can reduce costs with monitoring.

In conclusion, sedation with propofol plus fentanyl was more effective and had a shorter recovery time compared with sedation with midazolam plus fentanyl in cirrhotic patients. Propofol administration by gastroenterologist was safe. There were no differences in this study when complications in both groups were compared. Sedation with propofol and fentanyl can be safe and effective for UGIE in cirrhotic outpatients and is an alternative to midazolam and fentanyl.

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Appendix 1. The OAAS scale

Categories				Score
Responsiveness	**Speech**	**Facial expression**	**Eyes**	
Responds readly to name	Normal	Normal	Clear, no ptosis	5
Lethargic response to name	Mild Slowing or thickening	Mild relaxion	Glazed or mild ptosis	4
Responds only after name is called loudly and repeatedly	Slurring or proeminent slowing	Marked relaxion	Glazed and marked ptosis	3
Responds only after mild prodding or shaking	Few recognizable words	—	—	2
Does not respond to mild prodding or shaking	—	—	—	1