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Original Article

Propofol Versus Midazolam for Sedation in Patients With Cirrhosis Undergoing Upper Endoscopy: A Single-Blind Randomized Clinical Trial

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Abstract

Background: Patients with hepatic cirrhosis are frequently screened for the complications of portal vein hypertension using upper endoscopy. The current study aimed to compare the efficacy and safety of midazolam and propofol for sedation in patients with cirrhosis undergoing upper endoscopy.

Methods: This single-blind randomized clinical trial included 60 cirrhotic patients aged 18-80 years referred to Shahid Mohammadi hospital, Bandar Abbas, Iran from May 22, 2019, to May 21, 2020, for upper endoscopy. The age, gender, weight, and height of the patients were recorded, and they were randomized into two groups. Patients in the midazolam group (n=30) received 0.05 mg/kg midazolam for induction which continued with a 1 µg/kg/min dose, and those in the propofol group received 1 mg/kg propofol which continued with a 25-75 µg/kg/min dose. Blood pressure, oxygen saturation (SpO_2), respiratory rate (RR), and heart rate (HR) were measured before induction, immediately, 1, and 5 minutes after induction, and in the recovery unit. Finally, the time to reach the target sedation (Ramsay sedation scale ≥ 5), sedation duration, and recovery time were noted as well.

Results: Patients in both groups were comparable regarding age, gender, weight, and height. There were no significant differences between groups regarding hemodynamic parameters at any given time point, except for RR 1 minute after induction, which was significantly higher in the propofol group ($P=0.012$). Changes in HR from baseline to recovery were significant in both groups. Moreover, changes in SpO_2 from baseline to recovery were only significant in the midazolam group ($P<0.001$). The time to reach the target sedation and sedation duration were significantly lower in the propofol group ($P<0.001$ and $P=0.003$, respectively); however, there was no significant difference between groups with regard to the recovery time. Grade II encephalopathy (West Haven criteria) developed in one patient in the midazolam group.

Conclusion: Based on the results of the current study, although propofol was superior to midazolam for upper endoscopy in cirrhotic patients with respect to the time to reach the target sedation and sedation duration, the two drugs were rather comparable in terms of hemodynamic stability. However, hepatic encephalopathy with midazolam remains a major concern.

Keywords: Sedatives, Midazolam, Propofol, Cirrhosis, Endoscopy

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Background

Currently, liver cirrhosis is one of the most common gastrointestinal pathologies in adults and is among the leading causes of death around the world (1, 2). The etiological factors of this disease include alcohol abuse, nonalcoholic fatty liver disease, hepatitis B and C, and nonalcoholic steatohepatitis (1). Hepatic cirrhosis accounts for 800 000 deaths annually, accounting for 31% of deaths worldwide. In addition, the 5-year survival rate of these patients is 36% (3).

Patients with liver cirrhosis frequently undergo endoscopy for screening the side effects of portal vein hypertension, including esophageal varices. To alleviate the patient's pain, the endoscopy procedure is performed under sedation (4). Liver cirrhosis leads to the dysregulation of drug metabolism, protein synthesis, and hepatic blood flow, all of which affect the pharmacokinetics of the sedative drugs (5). Enhanced sedative effects

resulting from the higher plasma concentration of the drug or its longer sedative effects caused by delayed clearance can result in cardiopulmonary complications and worsen hepatic encephalopathy, leading to delayed recovery (4).

Midazolam or propofol with or without opioids are the most common sedative regimens used in endoscopy (6, 7). Midazolam is superior to older benzodiazepines due to its short onset of action and stronger anesthetic effects (8, 9). The mechanism of action of midazolam is through stimulating the gamma-aminobutyric acid (GABA) receptors, the major inhibitory neurotransmitter in the mammalian brain, leading to reduced anxiety, decreased muscle tone, sleep induction, and sedation, as well as having anticonvulsant effects. However, due to the hepatic metabolism of this drug, patients with liver failure are at risk of cardiopulmonary complications and worsening of hepatic encephalopathy (10). Propofol is a hypnotic agent and acts through decreasing the dissociation of GABA from GABA receptors in the brain. Propofol lacks an analgesic effect. The advantages of this drug include the rapid onset of action, short-term recovery, and rapid normalization of neuronal activities. The most important drawback of propofol is the induction of respiratory depression (11).

The results of some studies indicated that propofol is superior to midazolam with respect to the safety and efficiency of sedation in patients with cirrhosis undergoing endoscopy (5, 12, 13). Nevertheless, there is no guideline regarding the endoscopic actions for patients with cirrhosis (5). Taking the above-mentioned issues into account, this study aimed to compare the sedative effects of midazolam and propofol in patients with cirrhosis undergoing upper endoscopy.

Materials and Methods

Participants and Study Design

This single-blind randomized clinical trial included patients with cirrhosis aged 18-80 years who were scheduled for upper endoscopy. The inclusion criteria were Child-Pugh class A or B, Model for End-stage Liver Disease (MELD) score ≤ 24, and American Society of Anesthesiologists class II. Patients were recruited through convenience sampling between May 22, 2019, and May 21, 2020, from Shahid Mohammadi hospital, Bandar Abbas, Iran. On the other hand, the exclusion criteria were known allergy or hypersensitivity to sedative agents, significant respiratory disease, respiratory tract abnormalities, active neurologic disorders such as hepatic encephalopathy, advanced or decompensated liver failure (MELD score > 24, Child-Pugh class C, or Child-Pugh score > 10), alcohol consumption, and use of illegal drugs, sedatives, or narcotics. The sample size was calculated as at least 30 patients in each group based on the mean sedation time of 3.6 and 7.3 minutes in the propofol and midazolam groups, respectively, of the study by Weston et al (14), $\alpha = 0.05$, power of 95%, and the following formula:

$$\gamma^2 N = 2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \, d/2$$

All participants gave written informed consent to participate in the study. First, demographic and anthropometric features, including age, gender, weight, and height, were recorded for each patient. Then, they were randomized into two equal groups using block randomization. All patients were monitored using continuous electrocardiography, pulse oximetry, and continuous blood pressure (BP) measurements. Peripheral venous access was contrived for all patients. All participants received 3-5 L/mi of 100% oxygen through a nasal cannula, and 2 µg/kg fentanyl (Aburaihan Pharmaceutical Co., Iran) was administered for premedication. In the midazolam (M) group, 0.05 mg/kg midazolam (Exir Pharmaceutical Company, Iran) was administered for the induction of anesthesia and continued with a 1 µg/kg/min dose. In the propofol (P) group, 1 mg/kg propofol (B. Braun Medical Inc., Germany) was administered for the induction of anesthesia and continued with a 25-75 µg/kg/min dose. Further, 500 mL of a crystalloid solution (Ringer's lactate or normal saline) was administered during the procedure. Hemodynamic changes such as BP, heart rate (HR), respiratory rate (RR), and arterial oxygen saturation (SpO_2) were measured before induction, right after induction, 1 and 5 minutes after induction, and in the recovery unit. The Ramsay Sedation Scale (RSS) was used to assess sedation. The target sedation level was RSS ≥ 5. The time to reach the target level of sedation was recorded in seconds. The duration of sedation (minute) was noted as well. The whole procedure of anesthesia was identical for all patients and was performed by the same individual who was unaware of the patient groupings. All endoscopies were performed by the same gastroenterologist. After endoscopy, the patients were transferred to the recovery unit. Drug reactions were assessed during anesthesia and recovery. In the recovery unit, the severity of hepatic encephalopathy was evaluated using the West Haven criteria. Patients' length of stay in the recovery unit was also recorded, and participants were discharged from the recovery unit with Aldrete score > 8. The researcher in charge of patient assessments was blinded to their groupings. The primary outcome was the time to reach the target sedation, and secondary outcomes were the duration of sedation, recovery time, and drug side effects.

Data Analysis

The Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp.,

USA) was used for data analysis, and means, standard deviations, as well as percentages and frequencies were employed for the description of variables.

The chi-square test was applied to compare qualitative data. Quantitative variables were abnormally distributed based on the Kolmogorov-Smirnov normality test; thus, the Mann-Whitney test was utilized for their comparison between groups. Furthermore, the Friedman test was used to compare quantitative variables within groups, and P values < 0.05 were considered statistically significant.

Results

Initially, 71 patients were assessed for eligibility, of whom 6 declined to participate and 5 did not meet the inclusion criteria (Figure 1). The remaining 60 patients were randomized into two equal groups (midazolam and propofol). Patients in both groups were comparable regarding age, gender, weight, and height (Table 1).

Baseline hemodynamic parameters did not differ between groups (Table 2). Additionally, there was no significant difference between midazolam and propofol groups regarding hemodynamic parameters at any given time point, except for RT 1 minute after induction, which was significantly higher in the propofol group ($P = 0.012$). Changes in the HR from baseline to recovery were significant in both groups. Moreover, changes in SpO_2 from baseline to recovery were only significant in the midazolam group ($P < 0.001$, Table 2).

The time to reach the target sedation and sedation duration were significantly lower in the propofol group ($P < 0.001$ and $P = 0.003$, respectively); however, there was no significant difference between groups with respect to the recovery time (Table 3). Of note, grade II encephalopathy (West Haven criteria) developed in one patient in the midazolam group.

Table 1. Comparison of General Characteristics Between Groups

Variables	Propofol (n = 30)	Midazolam (n = 30)	*P* Value[a]
Age (years, mean ± SD)	51.51 ± 18.43	55.14 ± 13.79	0.634
Gender (N, %)			
Male	15 (50.0)	16 (53.3)	0.796[b]
Female	15 (50.0)	14 (46.7)	
Weight (kg, mean ± SD)	66.37 ± 12.14	65.65 ± 10.36	0.258
Height (cm, mean ± SD)	172.20 ± 6.86	172.80 ± 5.95	0.609

Note. N: Number; SD: Standard deviation.
[a] Analyzed by the Mann-Whitney test.
[b] Analyzed by the Chi-square test.

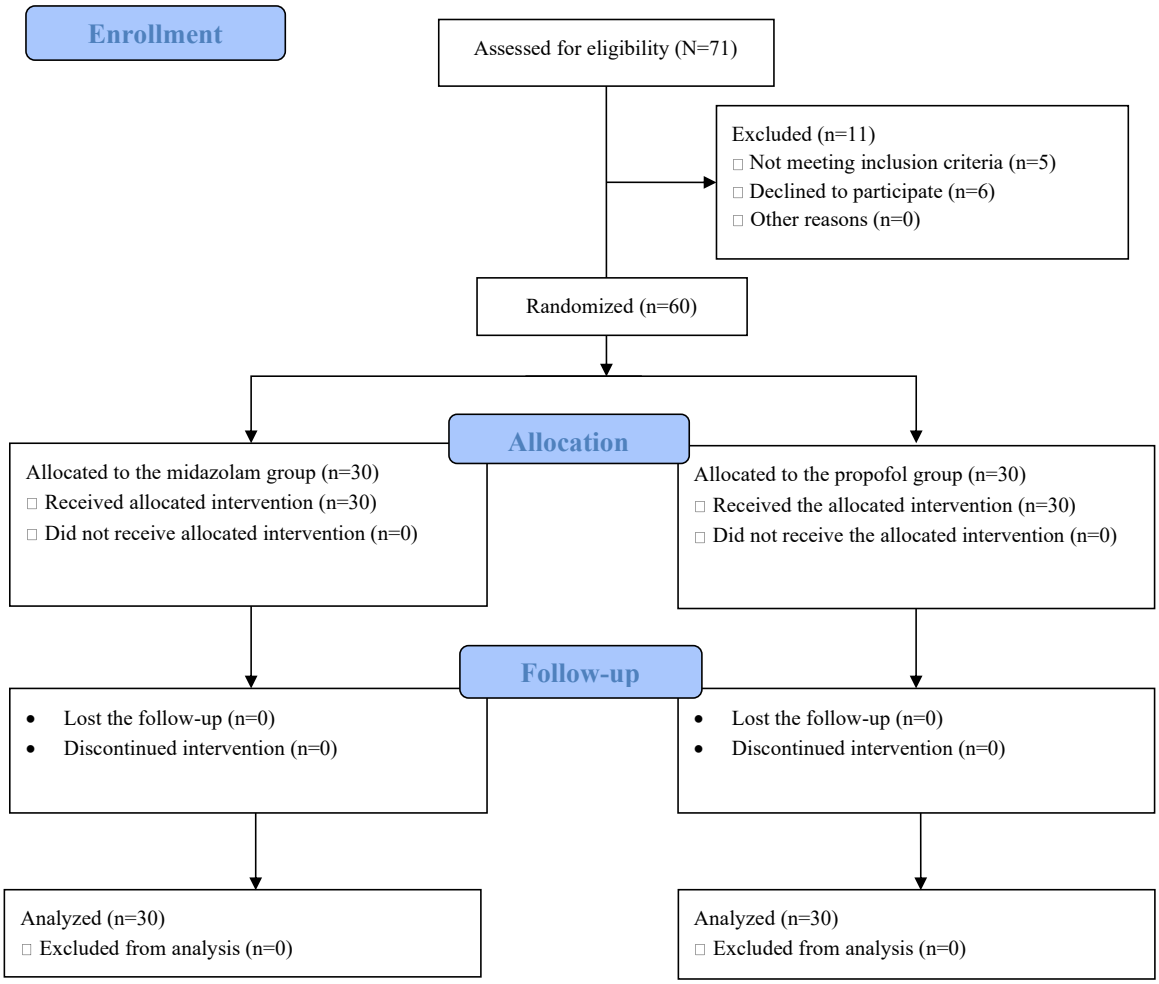

Figure 1. Details of Patient Enrollment, Intervention Allocation, and Analysis

Table 2. Comparison of Hemodynamic Changes Between Groups at Different Time Points*

	Time	Propofol (n = 30)	Midazolam (n = 30)	*P* Value[a]
SBP (mm Hg)	Before induction	124.83 ± 21.36	119.47 ± 10.18	0.611
	Immediately after induction	120.90 ± 20.84	119.20 ± 18.13	0.678
	At 1 minute	119.57 ± 19.79	120.53 ± 18.71	0.665
	At 5 minutes	119.07 ± 26.15	119.80 ± 13.46	0.357
	In the recovery unit	115.97 ± 25.07	120.47 ± 15.73	0.187
	P value[b]	0.133	0.132	
DBP (mm Hg)	Before induction	73.83 ± 12.47	71.60 ± 11.39	0.504
	Immediately after induction	75.53 ± 15.33	72.53 ± 15.31	0.381
	At 1 minute	74.23 ± 12.44	75.33 ± 14.21	0.964
	At 5 minutes	72.23 ± 14.99	71.93 ± 13.61	0.504
	In the recovery unit	71.47 ± 16.20	72.87 ± 12.91	0.790
	P value[b]	0.562	0.169	
HR (bpm)	Before induction	82.70 ± 10.90	79.33 ± 13.74	0.230
	Immediately after induction	88.20 ± 14.86	88.73 ± 14.54	0.756
	At 1 minute	88.77 ± 13.83	87.67 ± 15.50	0.486
	At 5 minutes	85.87 ± 13.73	78.53 ± 23.60	0.307
	In the recovery unit	83.90 ± 14.28	84.60 ± 16.55	0.711
	P value[b]	0.017	< 0.001	
RR (/min)	Before induction	14.90 ± 3.40	14.73 ± 2.45	0.845
	Immediately after induction	15.10 ± 3.43	13.80 ± 2.52	0.124
	At 1 minute	15.20 ± 2.76	13.40 ± 2.28	0.012
	At 5 minutes	14.07 ± 3.58	12.80 ± 2.26	0.238
	In the recovery unit	13.63 ± 4.27	13.53 ± 2.26	0.378
	P value[b]	0.770	0.151	
SpO2 (%)	Before induction	98.23 ± 2.78	97.53 ± 3.10	0.188
	Immediately after induction	96.80 ± 5.29	96.93 ± 3.05	0.185
	At 1 minute	96.87 ± 4.22	97.40 ± 2.34	0.538
	At 5 minutes	97.23 ± 4.30	97.33 ± 2.56	0.301
	In the recovery unit	97.97 ± 3.22	98.07 ± 2.21	0.472
	P-value[‡]	0.092	< 0.001	

Note. SD: Standard deviation; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; Bpm: Beats per minute; RR: Respiratory rate; SpO_2: Arterial oxygen saturation.
* Values are expressed in mean ± standard deviation (SD).
[a] Analyzed by the Mann-Whitney test.
[b] Analyzed by the Friedman test.

Table 3. Comparison of the Time to Reach the Target Sedation, Sedation Duration, and Recovery Time Between Groups

Variables	Propofol (n = 30)	Midazolam (n = 30)	*P* Value[a]
Sedation duration (minute) mean ± SD	11.70 ± 3.78	14.74 ± 3.19	0.003
Time to reach the target sedation (sec) mean ± SD	62.83 ± 41.74	102.67 ± 23.63	< 0.001
Recovery time (minute) mean ± SD	18.50 ± 7.29	20.33 ± 5.40	0.110

Note. SD: Standard deviation.
[a] Analyzed by the Mann-Whitney test.

Discussion

In the current study, in cirrhotic patients undergoing upper endoscopy, the time to reach the target sedation and sedation duration was significantly shorter with propofol compared to midazolam. Nevertheless, the recovery time was comparable between groups. In line with our findings, Tsai et al reported a shorter time to sedation with propofol (12). In addition, consistent with our results, Wahab et al demonstrated that the time to regain consciousness was significantly shorter with propofol (5), which corresponds to the significantly shorter sedation duration in our study. Nevertheless,

contrary to our findings, in a recent systematic review and meta-analysis of randomized clinical trials by Gaucho et al, the recovery time was significantly shorter with propofol in comparison to midazolam (15). Tsai et al also reported a shorter recovery time with propofol (12). This was also the case in the study by Wahab et al (5). The discrepancy between our study results and those of previous research regarding a significantly shorter recovery time with propofol can be due to the difference in the general characteristics of the study populations, doses of medications, measurement intervals, and underlying etiology of cirrhosis in the patients of different studies. Although our results regarding the recovery time did not confirm the findings of previous studies, what they reported adds to the superiority of propofol to midazolam for sedation in cirrhotic patients undergoing upper endoscopy.

Another finding of the current study was that all hemodynamic parameters were comparable between groups at any given time point, except for the RR which was significantly lower with midazolam 1 minute after induction, as well as significant SpO_2 changes in the midazolam group rather than in the propofol group. Decreased RR can be indicative of progression to respiratory depression, which can be of concern when administering propofol. In fact, respiratory depression is the most important side effect of propofol (11); however, our findings showed that RR was significantly higher with propofol 1 minute after induction. Moreover, Gaucho et al reported similar results with both propofol and midazolam regarding bradycardia and hypoxemia (15). The results of the study by Tsai et al (12), with respect to the similar incidence of hypotension, bradycardia, or hypoxemia in both the midazolam and propofol groups, are consistent with those of Gaucho et al (15). Nonetheless, while hypoxia and bradycardia were comparable between groups, the incidence of hypotension was significantly higher with propofol in the study by Zhang et al (9). Contrarily, hypotension was not a matter of concern in our study. The variety of findings among studies can mostly be justified by the difference in the definition of bradycardia, hypotension, and hypoxia, along with the difference in the underlying respiratory and cardiovascular status of the patients.

One important finding of this study was that grade II encephalopathy developed in one patient in the midazolam group. This potential adverse event was either not evaluated in previous studies or did not occur in any of their patients. Our study was not without limitations. The major limitation of the current study was its relatively small sample size; therefore, the results must be generalized with caution.

Conclusion

In the current study, propofol was superior to midazolam for upper endoscopy in cirrhotic patients with respect to the time to reach the target sedation and sedation duration. However, the two drugs were rather comparable in terms of hemodynamic stability. Nonetheless, encephalopathy did not occur with propofol, while it developed in one patient of the midazolam group. Overall, propofol appears to be a better option for sedation in cirrhotic patients undergoing upper endoscopy.

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Authors' Contribution

Conceptualization and Study Validation: MKB and MV
Implementation and Supervision: SB
Data Analysis and Interpretation: HD
Writing and Reviewing: SB
All authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no conflict of interests.

Consent for Publication

Not applicable.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was approved by the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1398.200) and is according to the statements of the Declaration of Helsinki. The trial has also been registered at the Iranian Registry of Clinical Trials (identifier: IRCT20201011048996N1) and is available at https://www.irct.ir/trial/51556.

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