Safety and effectiveness of midazolam for cirrhotic patients undergoing endoscopic variceal ligation

Hee Bum Jo, Jun Kyu Lee, Dong Kee Jang, Hyoun Woo Kang, Jae Hak Kim, Yun Jeong Lim, Moon-Soo Koh, Jin Ho Lee

Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University School of Medicine, Goyang, Korea

Cite this article as: *Jo HB, Lee JK, Jang DK, et al. Safety and effectiveness of midazolam for cirrhotic patients undergoing endoscopic variceal ligation. Turk J Gastroenterol DOI: 10.5152/tjg.2018.17589*

ABSTRACT

Background/Aims: *Endoscopic variceal ligation (EVL) is an established treatment for esophageal variceal bleeding. Midazolam (MDZ) is most commonly used for sedation during endoscopic procedures. However, adverse events (AEs) may occur more frequently in patients with cirrhosis due to altered MDZ metabolism.*

Materials and Methods: *We retrospectively reviewed the records of 325 patients with cirrhosis who received EVL.*

Results: *No significant differences were found in treatment outcome and procedure time among 151 patients in the MDZ group and 169 patients in the non-MDZ group. Desaturation (23.2% vs. 7.7%, p<0.01), bradycardia (22.5% vs. 17.2%, p=0.03), and hepatic encephalopathy (HE) (6.6% vs. 0.6%, p<0.01) were more common in the MDZ group than in the non-MDZ group. Logistic regression analyses revealed that an Eastern Cooperative Oncology Group (ECOG) score of ≥2 (p<0.01) and the use of MDZ (p<0.01) were associated with the development of overall AEs. An ECOG score of ≥2 (p=0.01), high serum creatinine level (p=0.02), and the use of MDZ (p<0.01) were significant risk factors for HE.*

Conclusion: *Extreme caution should be taken when sedating patients with cirrhosis receiving EVL due to the AEs associated with the use of MDZ.*

Keywords: *Liver cirrhosis, esophageal varices, hepatic encephalopathy, conscious sedation, midazolam, adverse events*

INTRODUCTION

Endoscopic variceal ligation (EVL) is an accepted treatment for esophageal variceal bleeding in patients with cirrhosis (1-4). Generally, patients who receive endoscopy, particularly for therapeutic purposes, are sedated to improve their procedural tolerability (5-7). Midazolam (MDZ) is one of the most commonly used sedative drugs with a short induction and recovery time (8-10). Moreover, the actions of MDZ can be antagonized quickly by the antidote, flumazenil in case of adverse events (AEs). The mechanism of MDZ is mediated via a gamma-aminobutyric acid neurotransmitter system in the brain, which is reportedly associated with the development of hepatic encephalopathy (HE) (11-13). Further, other AEs related to MDZ may occur more frequently in patients with cirrhosis due to the altered metabolism. However, data are limited regarding the sedation of patients with liver cirrhosis, particularly during EVL that needs proper sedation for a successful outcome. The safety and effectiveness of MDZ in patients with cirrhosis undergoing EVL were evaluated in the present study.

MATERIALS AND METHODS

Study population

The medical records of patients with cirrhosis who underwent EVL between October 2010 and December 2016 were reviewed retrospectively. Exclusion criteria comprised chronic use of benzodiazepines, overt HE, and state of cardiopulmonary dysfunction defined as follows: hypotension (systolic blood pressure<90 mm Hg and/or diastolic blood pressure<50 mm Hg), bradycardia (heart rate<55 beats per minute), and desaturation (<90% on pulse oximetry). Patients undergoing endoscopic screening were not included. Patients were divided into two groups according to the use of MDZ (MDZ group and non-MDZ group). In the MDZ group, a dose of 0.05 mg/kg was administered initially with additional doses of 1 mg every 3 min as necessary until the maximum dose of 0.075 mg/kg or 7.5 mg. In the non-MDZ group, patients received EVL without sedation. The level of sedation was regulated to facilitate EVL with minimal discomfort to the patients without cardiorespiratory compromise.

ORCID IDs of the authors: *H.B.J. 0000-0002-9136-3928; J.K.L. 0000-0002-2694-3598; D.K.J. 0000-0001-6642-6635; H.W.K. 0000-0003-3431-0827; J.H.K. 0000-0001-6270-3703; Y.J.L. 0000-0002-3279-332X; M.S.K. 0000-0002-3534-8459; J.H.L. 0000-0002-8013-3262.*

Corresponding Author: ***Jyun Kyu Lee; jeromee1971@yahoo.co.kr***

Received: ***September 11, 2017*** *Accepted:* ***February 9, 2018*** *Available online date:* ***June 25, 2018***

DOI: ***10.5152/tjg.2018.17589***

Table 2. Baseline characteristics

	Midazolam (n=151)	Non-midazolam (n=169)	p
Age, year	56.1±10.8	56.5±10.2	0.73
Sex (male/female)	129/22	134/27	0.15
Body mass index (kg/m^2)	23.6±3.7	22.9±3.2	0.09
Etiology			0.67
Alcohol (%)	75 (49.7%)	92 (54.4%)	
HBV (%)	62 (41.1%)	56 (33.1%)	
HCV (%)	7 (4.6%)	6 (3.6%)	
Others (%)	7 (4.6%)	15 (8.9%)	
Comorbidity			
Diabetes mellitus	48 (31.8%)	42 (24.9%)	0.17
Hypertension	14 (9.3%)	14 (9.3%)	0.76
COPD	0	0	0.99
Previous history of HE (%)	32 (21.1%)	55 (32.5%)	0.02
Ascites (%)	80 (53.0%)	88 (52.1%)	0.87
Hepatocellular carcinoma (%)	27 (17.9%)	31 (18.3%)	0.92
Child-Pugh classification			<0.01
Class A (%)	66 (43.7%)	49 (29.0%)	
Class B (%)	66 (43.7%)	78 (46.2%)	
Class C (%)	19 (12.6%)	42 (24.9%)	
MELD score	8.51 ± 4.82	9.04±5.82	0.52
ECOG≥2	43 (28.5%)	95 (56.2%)	<0.01
Active bleeding	38 (25.2%)	101 (59.8%)	<0.01
Paquet variceal grading system			<0.01
Grade 1	13 (8.6%)	11 (6.5%)	
Grade 2	73 (48.3%)	38 (22.5%)	
Grade 3	40 (26.5%)	77 (45.6%)	
Grade 4	25 (16.6%)	43 (25.4%)	
Laboratory findings			
White blood cell (/μL)	5.485.0±2.950.7	5.000.7±2.612.0	0.12
Hemoglobin (g/dL)	10.8±2.4	10.3±1.8	<0.01
Platelet (×10^3/μL)	85.1±45.9	75.2±46.3	0.06
Total bilirubin (mg/dL)	2.26±3.50	2.68±4.14	0.33
Albumin (g/dL)	3.3±0.6	3.0±0.5	<0.01
Prothrombin time (INR)	1.32±0.23	1.50±0.55	0.13
Aspartate aminotransferase (IU/L)	56.3±45.1	80.8±93.1	<0.01
Alanine aminotransferase (IU/L)	34.6±26.8	43.1±45.6	0.03
Creatinine (mg/dL)	0.83±0.25	0.79±0.21	0.16
Midazolam dose (mg)	4.6±1.4	NA	NA

COPD: chronic obstructive lung disease; MELD: Model for End-Stage Liver Disease; ECOG: Eastern Cooperative Oncology Group performance status; HBV: hepatitis B virus; HCV: hepatitis C virus; HE: hepatic encephalopathy; NA: data not available

Table 2. Baseline characteristics

	Midazolam (n=151)	Non-midazolam (n=169)	p
Primary			
Treatment success	145 (96.0%)	163 (96.4%)	0.52
Secondary			
Procedure time (min)	10.7±10.5	12.6±16.9	0.54
Adverse events	83 (55.0%)	78 (46.0%)	0.11
Desaturation	35 (23.2%)	13 (7.7%)	<0.01
Tachycardia	26 (17.2%)	45 (26.6%)	0.04
Bradycardia	34 (22.5%)	29 (17.2%)	0.03
Excessive vomiting	4 (2.8%)	2 (1.2%)	0.42
Others*	0	0	0.99
Hepatic encephalopathy	9 (6.6%)	1 (0.6%)	<0.01
Mortality within 30 days	1 (0.7%)	0 (0.0%)	0.29

*procedure discontinuation or necessity of mask ventilation was included

Each patient was monitored using pulse oximetry and noninvasive blood pressure measurement. Furthermore, the respiratory rate and level were monitored every 10 min during the procedure and in the recovery room. The level of consciousness was recorded on a 5-point Observer's Assessment of Awareness/Sedation Scale, wherein 1=awake, 2=somnolent/drowsy, 3=responsive to loud or repeated verbal stimuli, 4=responsive to physical/painful stimuli, and 5=no response to physical/painful stimuli (14).

Oxygen was supplied through a nasal cannula throughout the procedure and in the recovery room as needed. All the patients were hospitalized during the procedure and until full recovery. Patients were monitored at the intensive care unit if necessary. The Institutional Review Board gave approval for the present study. Written informed consents for voluntary participation were obtained from all the patients (DUIH-IRB 2013-101).

Endoscopic procedures

EVL was performed using a standard technique. In brief, EVL was started from the gastroesophageal junction and advanced proximally for patients who were undergoing elective therapy with 2 to 6 bands. Emergency EVL was performed for patients who had active esophageal bleeding within 12 h, using 1 or 2 bands at the bleeding point. All endoscopic procedures were performed with gastrointestinal videoscopes (GIF-H260 and EVIS-260 A/B; Olympus, Tokyo, Japan). Procedure time was de-

Table 3. Univariate and multivariate logistic regression analyses to identify risk factors for overall adverse events*

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age	0.979	0.958-0.999	0.04	0.979	0.957-1.001	0.06
Body mass index	1.029	0.965-1.096	0.39			
Child-Pugh class≥B	1.233	0.781-1.949	0.37			
MELD score	0.995	0.955-1.036	0.80			
ECOG≥2	2.628	1.665-4.148	<0.01	2.494	1.462-4.257	<0.01
Active bleeding	2.175	1.385-3.414	<0.01	1.079	0.452-2.572	0.86
Overnight procedure	1.306	0.675-2.526	0.43			
Ascites	1.024	0.660-1.588	0.92			
Previous history of HE	0.952	0.582-1.559	0.85			
White blood cell	1.000	1.000-1.000	0.27			
Hemoglobin	0.956	0.860-1.063	0.41			
Platelet	0.997	0.992-1.002	0.18			
Total bilirubin	1.032	0.971-1.096	0.31			
Albumin	0.542	0.363-0.807	<0.01	0.644	0.408-1.015	0.06
Prothrombin time	0.983	0.590-1.639	0.95			
Aspartate aminotransferase	1.006	1.002-1.010	<0.01	1.004	1.000-1.008	0.05
Alanine aminotransferase	1.006	1.000-1.013	0.06	0.996	0.986-1.006	0.40
Creatinine	1.601	0.613-4.177	0.34			
Procedure time	1.030	1.008-1.053	<0.01	1.010	0.987-1.032	0.40
Use of midazolam	1.424	0.916-2.213	0.12	2.340	1.406-3.893	<0.01

*variables with p<0.15 by univariate analysis were selected to enter into stepwise regression

OR: odds ratio; CI: confidence interval; MELD: Model for End-Stage Liver Disease; ECOG: Eastern Cooperative Oncology Group performance status; HE: hepatic encephalopathy

fined as the time from the passage of the endoscope through the cricopharyngeus muscle until removal of the endoscope. Esophageal varices were graded using the Paquet grading systems, wherein grade 0=no varices; grade 1=disappearing with insufflation; grade 2=larger, clearly visible, usually straight varices, not disappearing with insufflation; grade 3=more prominent varices, locally coil-shaped and partly occupying the lumen; and grade 4=tortuous, sometimes grape-like varices occupying the esophageal lumen (15).

Outcomes of interest and statistical analysis

The primary outcome of interest was treatment success. The secondary outcomes were procedure time, AEs, and mortality within 30 days. Treatment success was defined as successful ligation of the varices confirmed by follow-up endoscopy performed 48 h after the procedure. AEs were defined as the occurrence of any undesired events, and their relationship with MDZ could not be excluded.

HE was defined and graded according to the West Haven criteria, wherein grade 1=trivial lack of awareness, shortened attention span, impaired performance of addition, and euphoria or anxiety; grade 2=lethargy or apathy, minimal disorientation for time or place, subtle personality change, and inappropriate behavior; grade 3=somnolence to semi-stupor but responsive to verbal stimuli, confusion, and gross disorientation; and grade 4=coma (16). Hypoxemia was defined as oxygen saturation<90% and patient unresponsive for 15 s to jaw extension maneuver, verbal stimulus, or an increase in oxygen supplementation. Bradycardia was defined as a 25% decrease in initial heart rate or heart rate <55 beats per minute.

Risk factors and comorbidities affecting the development of AEs and HE were also evaluated. Expected risk factors were age, body mass index, stage of cirrhosis, grade of varices, ascites, history of HE, Eastern Cooperative Oncology Group (ECOG) performance status, active bleeding, overnight pro-

Table 4. Univariate and multivariate logistic regression analyses to identify risk factors for hepatic encephalopathy*

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age	1.014	0.959-1.072	0.63			
Body mass index	1.002	0.842-1.192	0.98			
Child-Pugh class≥B	2.594	0.551-12.218	0.40			
MELD score	1.049	0.959-1.148	0.30			
ECOG≥2	3.672	0.956-14.107	0.06	6.111	1.478-25.270	0.01
Active bleeding	2.347	0.673-8.182	0.22			
Overnight procedure	1.538	0.321-7.384	0.64			
Ascites	1.609	0.462-5.607	0.45			
Previous history of HE	1.004	0.260-3.876	0.99			
White blood cell	1.001	1.001-1.002	0.03	1.000	1.000-1.000	0.77
Hemoglobin	0.635	0.452-0.892	0.01	0.853	0.598-1.217	0.38
Platelet	1.003	0.991-1.015	0.67			
Total bilirubin	1.078	0.991-1.174	0.44			
Albumin	0.452	0.150-1.363	0.16			
Prothrombin time	1.084	0.338-3.477	0.89			
Aspartate aminotransferase	0.992	0.976-1.009	0.38			
Alanine aminotransferase	0.982	0.949-1.017	0.32			
Creatinine	17.723	2.979-105.435	<0.01	9.032	1.391-58.655	0.02
Procedure time	1.019	0.994-1.044	0.12	0.999	0.966-1.032	0.94
Use of midazolam	11.915	1.507-94.214	<0.01	16.889	2.033-140.312	<0.01

*variables with p<0.15 by univariate analysis were selected to enter into stepwise regression

OR: odds ratio; CI: confidence interval; MELD: Model for End-Stage Liver Disease; ECOG: Eastern Cooperative Oncology Group performance status; HE: hepatic encephalopathy

cedure, procedure times, and laboratory findings. Stage of cirrhosis was based on the Child-Pugh classification and Model for End-Stage Liver Disease. The ECOG performance status was scored as follows: 0=fully active, able to carry on all pre-disease performance without restriction; 1=restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2=ambulatory and capable of all self-care but unable to carry out any work activities up and approximately more than 50% of waking hours; 3=capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4=completely disabled and cannot carry on any self-care, totally confined to bed or chair; and 5=dead (17). Subgroup analyses were performed with patients who were in grade C according to the Child-Pugh classification and had active bleeding.

Differences between the groups in categorical variables were analyzed using the chi-square test with Yates correction or Fisher's exact test, as applicable. Mean values were expressed as mean ± standard deviation and compared using the Student's t-test. A p-value of <0.05 was considered statistically significant. Risk factors for the development of AEs were analyzed using logistic regression analysis. Variables with p<0.15 on univariate analysis were selected to enter into stepwise regression. Data were analyzed using Statistical Package for Social Sciences (SPSS) 18.0 for Windows (IBM Inc., Armonk, NY, USA).

RESULTS

Overall, 325 patients received EVL during the study period, and 5 ineligible patients were excluded. In conclusion, there were 151 patients in the MDZ group and 169 patients in the non-MDZ group. No differences in age, sex, body mass index, etiology of cirrhosis, comorbidity of chronic illnesses, and presence of ascites or hepatocellular carcinoma in both groups were found. However, there

Table 5. Subgroup analyses of patients in grade C based on the Child-Pugh classification for the development of overall adverse events*

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age	0.935	0.888-0.984	<0.01	0.953	0.900-1.008	0.10
Body mass index	1.034	0.888-1.205	0.67			
MELD score	0.998	0.920-1.082	0.96			
ECOG≥2	3.808	1.295-11.198	0.01	3.744	1.061-13.208	0.04
Active bleeding	3.167	1.110-9.032	0.03	0.316	0.016-6.414	0.45
Overnight procedure	1.867	0.404-8.617	0.47			
Ascites	0.593	0.149-2.354	0.51			
Previous history of HE	0.623	0.219-1.768	0.37			
White blood cell	1.000	1.000-1.000	0.25			
Hemoglobin	1.167	0.800-1.700	0.43			
Platelet	1.004	0.990-1.017	0.61			
Total bilirubin	1.049	0.970-1.135	0.22			
Albumin	0.197	0.045-0.860	0.02	0.242	0.042-1.383	0.11
Prothrombin time	0.769	0.356-1.660	0.47			
Aspartate aminotransferase	1.013	1.003-1.024	<0.01	1.009	0.999-1.019	0.09
Alanine aminotransferase	1.009	0.997-1.021	0.13	0.992	0.972-1.012	0.41
Creatinine	2.649	0.561-12.523	0.22			
Procedure time	1.077	1.004-1.157	0.02	1.039	0.969-1.114	0.28
Use of midazolam	1.222	0.413-3.618	0.71			

*variables with p<0.15 by univariate analysis were selected to enter into stepwise regression

OR: odds ratio; CI: confidence interval; MELD: Model for End-Stage Liver Disease; ECOG: Eastern Cooperative Oncology Group performance status; HE: hepatic encephalopathy

were fewer patients with a history of HE [32 (21.1%) out of 151 patients vs. 55 (32.5%) out of 169, p=0.02], Child-Pugh classification C [19 (12.6%) vs. 42 (24.9%), p<0.01], active bleeding [38 (25.2%) vs. 101 (59.8%), p<0.01], and variceal grade ≥3 [65 (43.0%) vs. 86 (57.0%), p<0.01] in the MDZ group than in the non-MDZ group (Table 1). Further, serum levels of hemoglobin and albumin were higher and those of aspartate aminotransferase and alanine aminotransferase were lower in the MDZ group than in the non-MDZ group. Mean dose was 4.6 ± 1.4 mg in the MDZ group.

No significant differences in treatment success and procedure time between the two groups were found. However, among AEs, desaturation [35 (23.2%) vs. 13 (7.7%), p<0.01], bradycardia [34 (22.5%) vs. 29 (17.2%), p=0.03], and HE [9 (6.6%) vs. 1 (0.6%), p<0.01] were more common in the MDZ group than in the non-MDZ group (Table 2). Conversely, there were fewer patients with tachycardia in the MDZ group than in the non-MDZ group [26 (17.2%) vs. 45 (26.6%), p=0.04]. Procedure discontinuation or mask ventilation was not needed in any of the patients. One case of mortality in the MDZ group was attributed to uncontrolled bleeding. An ECOG score of ≥2 (p<0.01) and the use of MDZ (p<0.01) were associated with the development of overall AEs in logistic regression analyses (Table 3). For HE, an ECOG score of ≥2 (p=0.01), high serum creatinine level (p=0.02), and the use of MDZ (p<0.01) were significant factors in multivariate analysis (Table 4). Overall, overt HE developed in 10 (3.1%) out of the 320 patients after EVL, and all of them recovered within 4 days.

In subgroup analyses with patients who were in grade C based on the Child-Pugh classification (Table 5) and actively bleeding (Table 6), an ECOG score of ≥2 (p=0.04) and old age (p=0.01) were associated with overall AEs, respectively.

Table 6. Subgroup analyses of patients with active bleeding for the development of overall adverse events*

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age	0.960	0.929-0.992	0.02	0.955	0.922-0.990	0.01
Body mass index	1.025	0.923-1.138	0.64			
Child-Pugh class≥B	0.826	0.390-1.750	0.62			
MELD score	0.993	0.930-1.061	0.83			
ECOG≥2	1.056	0.353-3.153	0.92			
Overnight procedure	0.742	0.354-1.557	0.43			
Ascites	0.787	0.398-1.559	0.49			
Previous history of HE	0.858	0.417-1.764	0.68			
White blood cell	1.000	1.000-1.000	0.78			
Hemoglobin	1.124	0.895-1.412	0.32			
Platelet	0.997	0.988-1.006	0.52			
Total bilirubin	1.172	0.981-1.400	0.08	1.096	0.905-1.327	0.35
Albumin	0.667	0.319-1.395	0.24			
Prothrombin time	1.176	0.276-5.013	0.83			
Aspartate aminotransferase	1.005	1.000-1.010	0.04	1.005	1.000-1.010	0.05
Alanine aminotransferase	1.002	0.995-1.010	0.52			
Creatinine	3.915	0.772-19.855	0.10	5.226	0.791-34.523	0.09
Procedure time	0.871	0.739-1.026	0.09	1.136	0.854-1.510	0.38
Use of midazolam	2.589	1.113-6.025	0.02	2.319	0.939-5.726	0.07

*variables with p<0.15 by univariate analysis were selected to enter into stepwise regression

OR: odds ratio; CI: confidence interval; MELD: Model for End-Stage Liver Disease; ECOG: Eastern Cooperative Oncology Group performance status; HE: hepatic encephalopathy

DISCUSSION

The results of 151 patients with cirrhosis who received MDZ sedation during EVL and 169 patients who did not receive sedation were compared in the present study. We found that desaturation, bradycardia, and HE were more common in the MDZ group than in the non-MDZ group during EVL in patients with cirrhosis. Development of overall AEs was associated with high ECOG score and the use of MDZ. AEs in HE developed in patients with high ECOG score, elevated serum creatinine level, and the use of MDZ.

In general, sedation is widely used for safe and successful procedure during endoscopic procedures (6). However, there are no specific guidelines for patients with cirrhosis although they frequently undergo endoscopy for screening and treatment of complications related to portal hypertension (18). Cooperation from patients is crucial for successful EVL, particularly for bleeding varices. Endoscopists frequently face a dilemma in this critical situation, particularly for patients who show uncontrollable agitation and aggressive behaviors. However, because concurrent hypovolemia is usual, there may be hesitation in using sedation for fear of cardiovascular AEs. In addition, even after a successful EVL, development of HE is a concern.

MDZ is widely used owing to its short half-life as well as anxiolytic and amnestic effects in a population with no cirrhosis (19). Following hepatic clearance, MDZ is metabolized by hydroxylation and conjugation with glucuronic acid (20). Decreased protein binding, intrinsic clearance, and metabolism combined with an increased volume of distribution contribute to a markedly prolonged half-life in patients with cirrhosis (20-22).

Conflicting results regarding the safety of MDZ in patients with cirrhosis were found. A few studies reported that subclinical HE is worse after MDZ administration (23-26). In contrast, other studies reported that MDZ may be used safely in patients with cirrhosis (18, 27, 28).

However, the correlation between MDZ and overt HE cannot be established because patients were discharged directly from an endoscopy unit or a recovery room and post-procedural monitoring was confined to 2 h in all the relevant studies. In our study, observation for an adequate period of time was possible because each patient was hospitalized until full recovery. Moreover, it could not be assessed whether risks of sedating patients with cirrhosis with MDZ outweighed the benefits of adequate procedure because none of the above included patients with cirrhosis with bleeding varices. Although Correia et al. included cases of EVL, the number is small (31 in the MDZ group) and does not include bleeding varices (18). In addition, our study population was homogenous because patients undergoing endoscopic screening were excluded. To the best of our knowledge, this is the first study that included patients with cirrhosis who received emergency procedures for bleeding varices.

Recently, sedation with propofol in patients with liver cirrhosis was reported (18, 25, 29, 30). Rapid recovery and improved patient comfort might be advantages associated with the use of propofol in patients with cirrhosis. However, propofol induces deep sedation without any antidotes and may increase the frequency of cardiovascular AEs compared with traditional agents (31). Furthermore, most of the data were obtained from less sick patients based on the American Society of Anesthesiologists classification≤3 or Child-Pugh classification A or B, and the safety of propofol in more serious patients was still a matter of concern.

The present study has several limitations. First, the patients from the non-MDZ group showed greater degree of severity in terms of previous history of HE, Child-Pugh classification, active bleeding, and variceal grade than those from the MDZ group. Nevertheless, AEs were more frequent in the MDZ group than in the non-MDZ group, suggesting a risk associated with the use of MDZ in patients with cirrhosis. Second, subclinical HE could not be evaluated because many of the patients received EVL in the emergency setting. Finally, the scales of patient discomfort could not be assessed in the present study.

In conclusion, extreme caution should be taken when sedating patients with cirrhosis receiving EVL because AEs are associated with the use of MDZ.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Dongguk University Ilsan Hospital.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.B.J., L.K.L, D.K.J.; Design - H.B.J., J.K.L., D.K.J.; Supervision - M.S.K., J.H.L.; Materials - D.K.J, H.W.K., J.H.K.; Data Collection and/or Processing - H.W.K., J.H.K., Y.J.L.; Analysis and/or Interpretation - H.W.K.; Literature Search - H.W.K.; Writing - J.K.L., D.K.J.; Critical Reviews - M.S.K., J.H.L.

Acknowledgements: The authors thank Mr. Ho Jung Lee for providing English proofreading of the manuscript.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Van Stiegmann G, Cambre T, Sun JH. A new endoscopic elastic band ligating device. Gastrointest Endosc 1986; 32: 230-3. [CrossRef]

2. Van Stiegmann G, Sun JH, Hammond WS. Results of experimental endoscopic esophageal varix ligation. Am Surg 1988; 54: 105-8.

3. Van Stiegmann G, Goff JS. Endoscopic esophageal varix ligation: preliminary clinical experience. Gastrointest Endosc 1988; 34: 113-7. [CrossRef]

4. Van Stiegmann G, Goff JS, Sun JH, Davis D, Bozdech J. Endoscopic variceal ligation: an alternative to sclerotherapy. Gastrointest Endosc 1989; 35: 431-4. [CrossRef]

5. Daneshmend TK, Bell GD, Logan RF. Sedation for upper gastrointestinal endoscopy: results of a nationwide survey. Gut 1991; 32: 12-5. [CrossRef]

6. Lichtenstein DR, Jagannath S, Baron TH, et al. Sedation and anesthesia in GI endoscopy. Gastrointest Endosc 2008; 68: 815-26. [CrossRef]

7. Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a nationwide survey. Am J Gastroenterol 2006; 101: 967-74. [CrossRef]

8. Keeffe EB. Sedation and analgesia for endoscopy. Gastroenterology 1995; 108: 932-4. [CrossRef]

9. Waring JP, Baron TH, Hirota WK, et al. Guidelines for conscious sedation and monitoring during gastrointestinal endoscopy. Gastrointest Endosc 2003; 58: 317-22. [CrossRef]

10. Riphaus A, Wehrmann T, Weber B, et al. S3-guidelines--sedation in gastrointestinal endoscopy. Z Gastroenterol 2008; 46: 1298-330. [CrossRef]

11. Schafer DF, Jones EA. Hepatic encephalopathy and the gamma-aminobutyric-acid neurotransmitter system. Lancet 1982; 1: 18-20. [CrossRef]

12. Lavoie J, Layrargues GP, Butterworth RF. Increased densities of peripheral-type benzodiazepine receptors in brain autopsy samples from cirrhotic patients with hepatic encephalopathy. Hepatology 1990; 11: 874-8. [CrossRef]

13. Olasmaa M, Rothstein JD, Guidotti A, et al. Endogenous benzodiazepine receptor ligands in human and animal hepatic encephalopathy. J Neurochem 1990; 55: 2015-23. [CrossRef]

14. Cohen LB, Delegge MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. Gastroenterology 2007; 133: 675-701. [CrossRef]

15 Paquet KJ. Prophylactic endoscopic sclerosing treatment of the esophageal wall in varices - a prospective controlled randomized trial. Endoscopy 1982; 14: 4-5. [CrossRef]

16. Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis 1970; 3: 282-98.
17. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-55. [CrossRef]
18 Correia LM, Bonilha DQ, Gomes GF, et al. Sedation during upper GI endoscopy in cirrhotic outpatients: a randomized, controlled trial comparing propofol and fentanyl with midazolam and fentanyl. Gastrointest Endosc 2011; 73: 45-51. [CrossRef]
19. Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. Clin Pharmacokinet 1999; 37: 17-40. [CrossRef]
20. Dundee JW, Halliday NJ, Harper KW, Brogden RN. Midazolam. A review of its pharmacological properties and therapeutic use. Drugs 1984; 28: 519-43. [CrossRef]
21. Steiner C, Sen S, Stange J, Williams R, Jalan R. Binding of bilirubin and bromosulphthalein to albumin: implications for understanding the pathophysiology of liver failure and its management. Liver Transpl 2004; 10: 1531-8. [CrossRef]
22. MacGilchrist AJ, Birnie GG, Cook A, et al. Pharmacokinetics and pharmacodynamics of intravenous midazolam in patients with severe alcoholic cirrhosis. Gut 1986; 27: 190-5. [CrossRef]
23. Assy N, Rosser BG, Grahame GR, Minuk GY. Risk of sedation for upper GI endoscopy exacerbating subclinical hepatic encephalopathy in patients with cirrhosis. Gastrointest Endosc 1999; 49: 690-4. [CrossRef]
24. Vasudevan AE, Goh KL, Bulgiba AM. Impairment of psychomotor responses after conscious sedation in cirrhotic patients undergoing therapeutic upper GI endoscopy. Am J Gastroenterol 2002; 97: 1717-21. [CrossRef]
25. Agrawal A, Sharma BC, Sharma P, Uppal R, Sarin SK. Randomized controlled trial for endoscopy with propofol versus midazolam on psychometric tests and critical flicker frequency in people with cirrhosis. J Gastroenterol Hepatol 2012; 27: 1726-32. [CrossRef]
26. Riphaus A, Lechowicz I, Frenz MB, Wehrmann T. Propofol sedation for upper gastrointestinal endoscopy in patients with liver cirrhosis as an alternative to midazolam to avoid acute deterioration of minimal encephalopathy: a randomized, controlled study. Scand J Gastroenterol 2009; 44: 1244-51. [CrossRef]
27. Trouvin JH, Farinotti R, Haberer JP, Servin F, Chauvin M, Duvaldestin P. Pharmacokinetics of midazolam in anaesthetized cirrhotic patients. Br J Anaesth 1988; 60: 762-7. [CrossRef]
28. Haq MM, Faisal N, Khalil A, Haqqi SA, Shaikh H, Arain N. Midazolam for sedation during diagnostic or therapeutic upper gastrointestinal endoscopy in cirrhotic patients. Eur J Gastroenterol Hepatol 2012; 24: 1214-8. [CrossRef]
29. Khamaysi I, William N, Olga A, et al. Sub-clinical hepatic encephalopathy in cirrhotic patients is not aggravated by sedation with propofol compared to midazolam: a randomized controlled study. J Hepatol 2011; 54: 72-7. [CrossRef]
30. Sharma P, Singh S, Sharma BC, et al. Propofol sedation during endoscopy in patients with cirrhosis, and utility of psychometric tests and critical flicker frequency in assessment of recovery from sedation. Endoscopy 2011; 43: 400-5. [CrossRef]
31. Sethi S, Wadhwa V, Thaker A, et al. Propofol versus traditional sedative agents for advanced endoscopic procedures: a meta-analysis. Dig Endosc 2014; 26: 515-24. [CrossRef]