Propofol alone prevents worsening hepatic encephalopathy rather than midazolam alone or combined sedation after esophagogastroduodenoscopy in compensated or decompensated cirrhotic patients

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Introduction

Esophagogastroduodenoscopy (EGD) is crucial in patients with cirrhosis in order to find gastric or esophageal varices, which are manifestations of portal hypertension. Moreover, in patients identified as having decompensated cirrhosis, EGD should be performed regularly even if there are no varices in the previous endoscopy, because there is a risk of worsening portal hypertension as the liver function deteriorates. Most guidelines recommend that EGD be performed when liver cirrhosis (LC) is first diagnosed. Depending on liver function, guidelines recommend EGD tracking every 1–2 years [1]. In particular, Korea is one of the countries with the highest incidence of gastric cancer in the world, so national surveillance for gastric cancer is recommended [2]. Therefore, patients with cirrhosis are also eligible for gastric cancer screening programs. The demand for sedation during endoscopies has been increasing for the convenience of endoscopists and patient comfort. In the USA, 98% of endoscopists use sedative drugs during EGD [3]. Midazolam is most commonly used in medical institutions, because it can result in forgetting of discomfort during the procedure due to anterograde amnesia with proper sedation. However, since midazolam is primarily metabolized in the liver, the metabolic rate of midazolam may be slowed in patients with chronic liver disease [4]. In addition, midazolam was reported as a risk factor for developing overt and covert hepatic encephalopathy (HE) [5]. On the other hand, propofol is another drug that can be used as a sedative for endoscopy and is not known to have pharmacokinetic differences in patients with renal failure or hepatic insufficiency. Therefore, there has been an increase in the use of...
propofol, which has a short duration of action and rapid recovery time in cirrhotic patients [6]. In one pilot study, endoscopy with propofol was reported to be safe for patients with cirrhosis [7]. In addition, two randomized control studies showed that propofol, compared to midazolam, was less likely to cause minimal HE (MHE) after endoscopy in cirrhotic patients [8,9].

However, most of the studies have been conducted in patients with LC who have good liver function, as assessed by Child-Pugh classification A (CTP A). There is very little research on sedative agent administration in decompensated LC (CTP B or C). Even though it is recommended to follow EGD more frequently in compensated or decompensated patients who develop ascites with liver disease and experience varix bleeding [10], there is a lack of information on which sedative drug and dose should be given to cirrhotic patients with decompensation.

The aim of this study was to determine a sedation strategy – using a safe sedative drug and the proper dose during endoscopy – to induce sufficient sedation and minimize worsening of HE after the procedure in cirrhotic patients with compensation or decompensation.

**Materials and methods**

**Study design**

Since 2018, the Hepatology Clinic at the Kosin University Gospel Hospital (KUGH) has conducted the number connection tests (NCT) before and 2 h after screening EGD to determine whether covert or overt HE has developed in patients with LC after sedation. Therefore, we retrospectively reviewed the medical records of patients diagnosed with cirrhosis, who were consecutively admitted to the hospital and received EGD with sedation from July 2018 to October 2019. This study design was approved by the Institutional Review Board/Ethics Committee of Kosin University Gospel Hospital (KUGH 2019-10-034). Informed consent was waived because of the retrospective study design.

 Decompensation was defined as a cirrhotic patient who had objectively identified ascites in computed tomography or abdominal sonography or who had evidence of varix bleeding within 3 months. Patients with a history of HE, previous trans-jugular intrahepatic portosystemic shunt, significant neurologic diseases and those with HE with baseline NCT >120 seconds were excluded [11,12].

**Study protocol**

Cirrhotic patients undergoing screening EGD had an NCT on the bedside from 8:00 a.m. to 9:00 a.m. The NCT is a test that evaluates the time needed to sequentially connect randomly placed numbers from 1 to 25 (NCT-A). To exclude the learning effect, we used two different types of NCT with a randomized distribution [13]. Initially, the trained nurse explained how to perform the NCT. Then the patient drew a line to connect the numbers from 1 to 25 as fast as possible. NCT results were categorized as grade 0 for 15–30 seconds, grade 1 (mild) for 31–50 seconds, grade 2 (moderate) for 51–80 seconds, grade 3 (severe) for 81–120 seconds and grade 4 (coma) for 120 seconds or longer [12].

The EGD of the liver disease patient was usually performed in KUGH between 9:00 a.m. and 11:00 a.m. After the EGD, close observation was performed in the recovery room for 20 minutes before return to the ward. Two hours after completion of the endoscopy with sedation, follow-up NCT was done at the bedside again.

Each EGD with sedation was performed by one of two hepatologists who received endoscopic certification from the Korean Society of Gastrointestinal Endoscopy (J.J. and K.I.S.). Cases of unexpected bleeding, inevitable varix bleeding ligation or endoscopic variceal obliteration were excluded from the study. The sedation level was determined by the endoscopist and the assisting nurse at the time. After the sedative drug was administered, the EGD began when moderate sedation (patient responds to verbal stimulation with stable vital signs) was induced [14]. The total EGD time was calculated from the time when the endoscope was inserted into the oral cavity until the time when the endoscope was withdrawn.

According to the hepatologist’s judgment, the endoscopic sedation was performed using propofol alone, midazolam alone, or combined (propofol + midazolam).

**Statistical analysis**

According to the normality test results, pre-NCT and post-NCT results were analyzed with the Wilcoxon signed-rank test. To compare the three groups according to the type of drugs used, one-way analysis of variance or the Kruskal–Wallis test was performed with continuous variables and linear by linear association was performed with categorical variables.

The Kruskal–Wallis test was used to compare delta-NCT according to the three sedation methods. Post hoc analysis was performed using the Mann–Whitney test. Multiple regression analysis was performed to find factors associated with delta-NCT.

Statistical significance was determined as $P < 0.05$. In the post-hoc test, Bonferroni’s method was used to determine the statistical significance at $P < 0.017$. SPSS software version 23 (IBM Corp., Armonk, New York, USA) was used.

**Results**

**Baseline characteristics of the cirrhotic patients**

From July 2018 to September 2019, 71 cirrhotic patients were consecutively admitted for a screening endoscopy with sedation. Two patients did not undergo NCT after EGD because of unexpected bleeding. Two patients had baseline NCT >120 seconds. Therefore, a total of 67 patients were analyzed in this study (Fig. 1).

The mean age was 53.8 ($\pm$9.91) and 49 (73.1%) of the patients were male. Forty-two (62.7%) patients have been educated for more than 12 years. The mean body weight was 64.2 ($\pm$14.19) kg, 19 (28.4%) patients had diabetes and 15 (22.4%) had hypertension. HBsAg positive was found in 20 (29.9%) patients and anti-HCV positive was found in seven (10.4%). Fifty-two patients had cirrhosis that was related to alcohol. On the day of the EGD, patients with ascites or varix bleeding within the last 3 months were diagnosed with decompensation. A total of 45 (67.2%) patients were diagnosed with decompensated LC (Table 1).
Endoscopy with sedation in all cirrhotic patients

Endoscope procedure time

The mean duration of EGD in 67 patients with LC was 313.9 (±194.36) seconds. Sedation was performed with propofol alone, midazolam alone or combined propofol + midazolam. Propofol alone sedation was performed in 22 patients and the mean EGD time was 328.8 (±225.49) seconds. Midazolam alone was used in 20 patients and the mean EGD time was 317.5 (±182.52) seconds. There were 25 patients who underwent combined propofol + midazolam sedation with a mean EGD time of 297.9 (±180.38) seconds (Table 2). No difference in endoscopy time was observed according to the three kinds of sedation methods ($P = 0.880$).

Process of sedation

Sedation was assessed by the endoscopist and assistant nurse. When the sedation was induced appropriately, the EGD was started. The degree of sedation aimed for moderate sedation/...
The delta values for pre-endoscopic NCT and post-endoscopic NCT were compared according to sedation method. In the propofol alone group, delta-NCT was 2.1 (±11.80) seconds, in the midazolam alone group 13.4 (±20.02) and in the combined propofol + midazolam group 12.6 (±16.79). There was a statistically significant difference in delta-NCT between the three groups \((P = 0.024)\). Post-hoc analysis showed there was a significant difference in delta-NCT between the propofol alone and combined groups \((P = 0.012)\) (Fig. 3).

Among three groups according to sedation strategy, no statistically significant differences in age, sex and education level were found (Table 1). The ages were 55.2, 59.1 and 53.8 years in propofol alone, midazolam alone and combined groups, respectively \((P = 0.250)\). The sexes were 16 \((72.7\%)\), 15 \((75.0\%)\) and 18 \((72.0\%)\) males in the propofol alone, midazolam alone and combined groups, respectively \((P = 0.250)\). Therefore, NCT results could be interpreted independently of age, sex and education.

Based on the baseline NCT results, among all cirrhotic patients, nine \((13.4\%)\) were grade 0, 33 \((49.3\%)\) were grade 1, 21 \((31.3\%)\) were grade 2 and four \((6.0\%)\) were grade 3. Among the decompensation patients, six \((13.3\%)\) were grade 0, 20 \((44.4\%)\) were grade 1, 15 \((33.3\%)\) were grade 2 and four \((8.9\%)\) were grade 3.

**Endoscopy with sedation in decompensated cirrhotic patients**

In 45 patients diagnosed with decompensated cirrhosis, the pre-endoscopic NCT was 50.4 (±22.13) seconds. The NCT performed 2 h after sedation was 61.3 (±32.42) seconds. There was a statistically significant difference between the NCT performed before and after endoscopy with sedation \((P = 0.0003)\) (Fig. 4a).

### Table 2. Endoscopy with sedation in cirrhotic patients

| Sedation strategy | All (N = 67) | Propofol (n = 22) | Midazolam (n = 20) | Combined (n = 25) | \(P\) value |
|-------------------|-------------|------------------|-------------------|------------------|------------|
| Sedative drug, mean (±SD) | | | | | |
| Propofol (mg) | 32.8 (±25.51) | 52.3 (±16.31) | - | 42.0 (±15.00) | |
| Propofol/kg (mg/kg) | 0.82 (±0.29) | 0.80 (±0.29) | 0.76 (±0.28) | 0.86 (±0.28) | |
| Midazolam (mg) | 2.6 (2.14) | - | 4.7 (±0.73) | 3.2 (±1.39) | |
| Midazolam/kg (mg/kg) | 0.08 (±0.02) | 0.08 (±0.02) | 0.05 (±0.02) | 0.05 (±0.02) | |
| EGD duration (seconds) | 313.9 (±194.36) | 328.8 (±225.49) | 317.5 (±182.52) | 297.9 (±180.38) | 0.880 |
| NCT, mean (±SD) | | | | | |
| Before EGD (seconds) | 48.2 (±20.18) | 47.3 (±19.71) | 50.3 (±20.56) | 47.4 (±20.99) | 0.767 |
| 2 h after EGD (seconds) | 57.6 (±29.13) | 49.4 (±21.79) | 63.7 (±33.17) | 60.0 (±30.79) | 0.240 |
| Delta-NCT (seconds) | 9.4 (±16.99) | 2.1 (±11.80) | 13.4 (±20.02) | 12.6 (±16.79) | 0.024 |
| HE (grade) | | | | | |
| Grade 0 | 9.0 (13.4) | 2.0 (9.1) | 3.0 (15.0) | 4.0 (16.0) | |
| Grade 1 | 32.0 (49.3) | 13.0 (59.1) | 9.0 (45.0) | 11.0 (44.0) | |
| Grade 2 | 21.0 (31.3) | 6.0 (27.3) | 6.0 (30.0) | 9.0 (36.0) | |
| Grade 3 | 4.0 (6.0) | 1.0 (4.5) | 2.0 (10.0) | 1.0 (4.0) | |
| Grade 4 | 0.0 (0.0) | 0.0 (0.0) | 0.0 (0.0) | 0.0 (0.0) | |
| 2 h after EGD (n %) | | | | | |
| Grade 0 | 7.0 (10.4) | 4.0 (18.2) | 2.0 (10.0) | 1.0 (4.0) | 0.238 |
| Grade 1 | 26.0 (38.8) | 9.0 (40.9) | 5.0 (25.0) | 12.0 (48.0) | |
| Grade 2 | 26.0 (38.8) | 8.0 (36.4) | 9.0 (45.0) | 9.0 (36.0) | |
| Grade 3 | 6.0 (9.0) | 1.0 (4.5) | 3.0 (15.0) | 9.0 (36.0) | |
| Grade 4 | 2.0 (3.0) | 0.0 (0.0) | 1.0 (5.0) | 1.0 (4.0) | |
| Aggravation of HE, n (%) | 22.0 (32.8) | 4.0 (18.2) | 8.0 (36.0) | 10.0 (40.0) | 0.122 |

EGD: esophagogastroduodenoscopy; HE, hepatic encephalopathy; NCT, number connection test.

analgesia (purposeful response to verbal or tactile simulation, spontaneous ventilation and maintained cardiovascular function) as suggested by the ASA [14]. All patients underwent pre-oxygenation before receiving the sedation. Vital signs (pulse, \(O_2\) saturation) were continuously checked through the endoscopic procedure. After the EGD, the patient was observed in the recovery room for about 20 minutes and then returned to the ward. If additional sedation was needed during the endoscopy, the sedation medication was administered according to the physician’s order.
Number connection test according to sedative method

In the propofol alone group, the NCT performed before sedation was 49.2 (±22.92) seconds and the NCT performed after sedation was 52.3 (±24.90) seconds (P = 0.4548). In the midazolam alone group, the NCT before sedation was 52.8 (±21.19) seconds; in the midazolam alone group, the pre-NCT was 47.3 (±19.71) seconds and post-NCT was 49.4 (±21.79) seconds (P = 0.6389). In the combined propofol + midazolam group, the pre-NCT was 49.0 (±23.68) seconds and post-NCT was 64.6 (±37.94) seconds (P = 0.0034) (Fig. 4).

Delta-number connection test according to sedative methods

In the propofol alone group, delta-NCT was 3.1 (±12.87) seconds; in the midazolam alone group, delta-NCT was 13.4 (±20.02) in the midazolam alone group, and 12.6 (±16.78) in the combined propofol + midazolam group. There was a statistically significant difference in delta-NCT between the three groups (P = 0.024).

Dose of sedative drug

The propofol alone group received 50.7 (±17.74) mg at 0.85 (±0.31) mg per kg. The midazolam alone group received 4.8 (±0.68) mg at 0.08 (±0.01) mg per kg. In the combined propofol + midazolam group, propofol was given 45.3 (±16.41) mg at 0.69 (±0.28) mg per kg. Midazolam was administered using 3.4 (±1.40) mg at 0.05 (±0.02) mg per kg (Table 3).
Risk factors associated with delta-number connection test

In simple regression analysis of all 67 patients with LC, serum sodium, sedation method and HTN correlated significantly with delta-NCT. In the result of multiple regression analysis, serum sodium was significantly correlated with delta-NCT ($r = 0.3594$, $P = 0.0028$) (Fig. 6).

Discussion

In this study, propofol alone was the safest sedative strategy in cirrhotic patients during EGD regardless of compensation or decompensation. The covert or overt HE did not worsen at 2 h after sedation in propofol alone group. Compared with the midazolam alone or combined propofol + midazolam groups, propofol alone was found to achieve the same level of sedation but was least likely to worsen covert or overt HE at 2 h after sedation. Even in decompensated LC patients, propofol alone did not appear to significantly induce HE after sedation compared to midazolam alone or combined sedation.

Midazolam is a protein-bound benzodiazepine characterized by a short-term hypnotic action and an elimination half-life of less than 2 h [15]. However, in cirrhotic patients, midazolam has a markedly prolonged half-life because of decreased protein binding, impaired intrinsic clearance, and increased volume of distribution [16]. In contrast, propofol produces sedative effect through the GABA receptor. Even after prolonged infusion, propofol reveals a rapid onset and offset [17]. Clinically, in cirrhotic
patients, propofol revealed shorter duration and recovery times than midazolam [6]. Therefore, propofol is preferred to midazolam in patients with cirrhosis. However, there is a limited data about how much dose of propofol can be administered in patients with cirrhosis.

This study showed the dose of propofol that induced an appropriate level of sedation without causing covert or overt HE. The effective and safe dose of propofol was 0.82 (±0.29) mg per kg for EGD with sedation in patients with LC. Based on this result, the optimal dose of propofol alone for decompensated LC was 0.85 (±0.31) mg per kg. There was no significant difference in propofol dose among cirrhotic patients with compensation or decompensation.

In our study, the prevalence of MHE corresponding to grade 0 was 13.4% and the prevalence of covert HE classified as grade 0–1 was 62.7%. Although diagnosing covert or MHE with just one set of NCT results is unreasonable, this result suggests a prevalence of covert and MHE in real clinical practice. Moreover, EGD with sedation was also performed in patients with grade 2 or 3 of HE based on NCT. In other words, patients who have covert HE, which is a risk for overt HE, could also undergo EGD with sedation in clinical practice. Indeed, in our study, the number of patients whose grades worsened after the EGD with sedation was 32.8% (22 patients). The grades were worsened in 18.2% (4) of the propofol alone patients, but in 40% of patients in the midazolam alone and combined propofol + midazolam groups, respectively. Although there was no statistical significance, propofol alone tended to be safer than the other sedation methods (P = 0.122).

Especially, serum sodium level was identified as a risk factor related to the change in delta-NCT. Lower serum sodium levels were associated with an increase in delta-NCT. In patients with advanced LC, hyponatremia (primarily dilutional hyponatremia) is a common complication. Dilutional hyponatremia is related to

### Table 3. Endoscopy with sedation in decompensated cirrhotic patients

| Sedation strategy          | ALL (N = 45) | Propofol (n = 14) | Midazolam (n = 16) | Cimbined (n = 15) | P value |
|----------------------------|--------------|------------------|-------------------|------------------|---------|
| Age                        | 55.2 (±9.90) | 55.86 (±7.58)    | 58.75 (±11.81)    | 50.73 (±9.90)    | 0.072   |
| Body weight                | 64.4 (±13.89)| 62.26 (±12.34)   | 63.38 (±13.47)    | 67.52 (±15.96)   | 0.874   |
| Laboratory result, mean (±SD) | 5575.3 (±4696.77) | 4727.1 (±2920.43) | 7268.1 (±6999.52) | 4561.3 (±1954.96) | 0.220 |
| Hemoglobin (g/dl)          | 11.2 (±1.86) | 11.0 (±1.99)     | 11.5 (±1.92)      | 10.9 (±1.72)     | 0.708   |
| Platelet (x10^3/μl)        | 88.5 (±47.01)| 107.2 (±60.99)   | 89.2 (±38.92)     | 70.2 (±34.01)    | 0.132   |
| PT (INR)                   | 1.5 (±0.35)  | 1.5 (±0.41)      | 1.5 (±0.35)       | 1.5 (±0.32)      | 0.653   |
| Albumin (g/dl)             | 3.0 (±0.47)  | 3.0 (±0.57)      | 2.9 (±0.49)       | 3.1 (±0.31)      | 0.201   |
| Total bilirubin (mg/dl)    | 4.0 (±3.15)  | 3.0 (±2.11)      | 3.8 (±2.35)       | 5.1 (±4.35)      | 0.384   |
| Na (mEq/L)                 | 135.3 (±3.62)| 134.6 (±2.34)    | 134.8 (±2.34)     | 136.4 (±3.78)    | 0.368   |
| Ammonia (μMol/L)           | 68.6 (±21.71)| 72.2 (±25.02)    | 68.0 (±23.78)     | 65.9 (±16.53)    | 0.667   |
| EGD duration               | 305.3 (±197.54)| 317.3 (±219.55)  | 287.7 (±169.53)   | 312.9 (±215.70)  | 0.934   |
| Sedative drug, mean (±SD)  |              |                  |                   |                  |         |
| Propofol (mg)              | 50.7 (±17.74)| -                | 45.3 (±16.41)     |                  |         |
| Propofol/kg (mg/kg)        | 0.85 (±0.31) | -                | 0.89 (±0.28)      |                  |         |
| Midazolam (mg)             | -            | 4.8 (±0.68)      | 3.4 (±1.40)       |                  |         |
| Midazolam/kg (mg/kg)       | 0.08 (±0.01) | -                | 0.05 (±0.02)      |                  |         |
| NCT, mean (±SD)            |              |                  |                   |                  |         |
| Before EGD (seconds)       | 50.4 (±22.13)| 40.2 (±22.92)    | 52.8 (±21.19)     | 49.0 (±23.68)    | 0.748   |
| 2 h after EGD (seconds)    | 61.3 (±32.42)| 52.3 (±24.90)    | 66.1 (±33.05)     | 64.6 (±37.94)    | 0.467   |
| Delta-NCT (seconds)        | 10.9 (±18.82)| 3.1 (±12.87)     | 13.3 (±20.41)     | 15.5 (±20.56)    | 0.164   |
| HE (grade)                 |              |                  |                   |                  | 0.933   |
| Before endoscopy, n (%)    |              |                  |                   |                  |         |
| No                         | 6.0 (13.3)   | 1.0 (7.1)        | 2.0 (12.5)        | 3.0 (20.0)       |         |
| Grade 1                    | 20.0 (44.4)  | 8.0 (57.1)       | 7.0 (43.8)        | 5.0 (33.3)       |         |
| Grade 2                    | 15.0 (33.3)  | 4.0 (28.6)       | 5.0 (31.3)        | 6.0 (40.0)       |         |
| Grade 3                    | 4.0 (8.9)    | 1.0 (7.1)        | 2.0 (12.5)        | 1.0 (6.7)        |         |
| Grade 4                    | 0.0 (0.0)    | 0.0 (0.0)        | 0.0 (0.0)         | 0.0 (0.0)        |         |
| 2 h after endoscopy, n (%) |              |                  |                   |                  | 0.402   |
| No                         | 4.0 (8.9)    | 2.0 (14.3)       | 1.0 (6.3)         | 1.0 (6.7)        |         |
| Grade 1                    | 15.0 (33.3)  | 4.0 (28.6)       | 4.0 (25.0)        | 7.0 (46.7)       |         |
| Grade 2                    | 18.0 (40.0)  | 6.0 (42.9)       | 8.0 (50.0)        | 4.0 (26.7)       |         |
| Grade 3                    | 7.0 (15.6)   | 1.0 (7.1)        | 3.0 (18.8)        | 3.0 (20.0)       |         |
| Grade 4                    | 1.0 (2.2)    | 1.0 (0.0)        | 0.0 (0.0)         | 0.0 (0.0)        |         |

EGD, esophagogastroduodenoscopy; HE, hepatic encephalopathy; NCT, number connection test.

**Fig. 6.** Hyponatremia is associated with an increased delta-NCT. In simple regression analysis of all 67 patients with liver cirrhosis, serum sodium, sedation method and HTN correlated significantly with delta-NCT. Multiple regression analysis showed serum sodium was significantly correlated with delta-NCT (r = 0.3594, P = 0.0028).
hypoalbuminemia and portal hypertension in cirrhotic patients. Its complications include spontaneous bacterial peritonitis, hepatorenal syndrome and HE [18]. Therefore, our study could suggest that hyponatremia may not only predict liver function, but may also be a risk factor that aggravates HE after endoscopy with sedation. Therefore, special clinical attention may be needed to watch for HE development after sedation in LC patients with hyponatremia.

There are several limitations in this study. First, only one set of NCT was performed to diagnose HE before and after EGD with sedation. In order to diagnose covert-HE in cirrhosis patients, it is recommended to use the Neuropsychological tests package [19]. However, various types of tests are not performed easily in the clinic. Therefore, a simple and reliable test should be developed in the future. Second, the educational status patients were not considered. It is well known that neuropsychological tests could be influenced by several compounding factors including age, sex and educational status [20]. Therefore, subsequent studies should include the amount of education. Third, the depth of sedation was determined based on the subjective judgment of the endoscopist and assistant nurse. Although this is a commonly used method in most clinical practice, it is not objective, which limits the reliability of this study. It is necessary to monitor the appropriate depth of sedation with objective measurements in the future.

In conclusion, propofol alone could be a good sedative strategy in LC patients with compensation or decompensation to induce the appropriate depth of sedation without aggravation of covert or overt HE. Clinically, 0.82–0.85 mg/kg of propofol is considered to be an appropriate dose in cirrhotic patients. In addition, physicians will need to pay close attention to cirrhotic patients with hyponatremia, which could be a risk factor for developing or worsening HE after EGD with sedation.

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Conflicts of interest
There are no conflicts of interest.

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