Sub-Clinical Hepatic Encephalopathy in Cirrhotic Patients Subjected to Sedation with either Propofol or Midazolam.

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Background and study aim: Patients with hepatic impairment are at higher risk for sedation complications. This study aims to determine the impact of propofol in comparison to midazolam on the occurrence of sub-clinical hepatic encephalopathy in liver cirrhotic patients undergoing upper gastrointestinal endoscopy (UGE).

Patients and Methods: The study population involved 70 patients. Group A included 10 non-hepatic patients who underwent UGE without sedation. Group B included 30 patients with CLD who received midazolam. Group C included 30 patients with CLD who received propofol. The level of encephalopathy was determined by the number connection test (NCT).

Results: In group B there was a mild decrease in systolic blood pressure during and after than before UGE with compensatory tachycardia. Also, there was some decrease in oxygen saturation during UGE (>90%) which resolved after oxygen flow. Patients of group C showed a decrease in systolic blood pressure at the onset of injection of propofol with mild tachycardia. There was a mild decrease in oxygen saturation during the procedure more significant than what happened in the midazolam group with no need for intubation. Regarding NCT one hour after and delta change of NCT, they showed a significant increase in group B versus group C. Times of procedure and recovery were significantly prolonged in group B in comparison to group C.

Conclusion: Midazolam exacerbates sub-clinical encephalopathy. The hypotension and tachycardia during the procedure were more significant in the midazolam group than in the propofol group. Subjects receiving propofol showed shorter induction, time of procedure, and recovery periods .

INTRODUCTION

Hepatic encephalopathy is an acute or chronic neurological disorder due to liver disease **[1]**. Sub-clinical hepatic encephalopathy or minimal hepatic encephalopathy (MHE), shows measurable neuropsychological disorders, but with normal neurological and mental status on clinical examination **[2, 3]**.

Upper gastrointestinal endoscopy (UGE) needs to be done regularly in chronic liver disease (CLD) patients for management and follow-up of esophageal varices, gastric varices, and portal hypertensive gastropathy which are complications due to portal hypertension **[4]**. Sedation is needed during this procedure to help the patient's tolerance **[5]**.

Patients with CLD are at risk of sedation complications during UGE. This is attributed to the metabolization of some of these sedative drugs in the liver, as well as due to the possible hemodynamic changes that are associated with the anesthetic drugs, due to higher plasma levels and prolonged effects of these drugs due to their delayed clearance **[6]**.

Midazolam is a benzodiazepine that is frequently used for mild sedation in the general population undergoing UGE **[7]**. It is anxiolytic and amnesic with a half-life of <6 hours [8]. CLD patients are at risk for neurological and respiratory complications due to

Production of active metabolites with different half-lives [9].

Propofol is a short-acting anesthetic drug that can be used drug during UGE. In comparison to benzodiazepines, it has convenient pharmacokinetic properties **[10]**.

This study aims to determine the impact of propofol in comparison to midazolam on the occurrence of sub-clinical hepatic encephalopathy in liver cirrhotic patients undergoing UGE.

PATIENTS AND METHODS

Study population

We conducted a retrospective observational study, comprising data from 70 Egyptian patients; male and female (aged 17 to 65years) collected from the endoscopy center of Ain Shams University Hospital, Cairo, Egypt, from December 2014; 60 patients were hepatic patients with CLD regardless of etiology (Child-Pugh class A, B or C) and 10 patients non-hepatic who underwent diagnostic or therapeutic UGE.

Inclusion criteria

All patients were matched for gender, age, and body mass index (BMI) and divided into three groups. Group A included 10 control non-hepatic patients who underwent UGE without sedation (neither propofol nor midazolam) for medical conditions other than liver diseases. Group B included 30 patients with CLD who received midazolam for sedation. Group C included 30 patients with CLD who received propofol for sedation.

All patients were subjected to complete blood count, liver and renal profile investigations, number connection test before and after the procedure, estimation of time to recovery and time of the procedure, and hemodynamic parameters (blood pressure, pulse, respiratory rate, and oxygen saturation) before, during and after sedation.

Exclusion criteria

Patients with psychiatric disease, active neurological disease, overt hepatic encephalopathy, alcohol or drug abuse, active respiratory illness, gastrointestinal hemorrhage, hepatocellular carcinoma, and allergy to sedative drugs were excluded from the study.

Technique

The number connection test (NCT) defines the time required to connect sequentially the randomly placed circles labeled from 1 to 25. The degree of encephalopathy was determined according to the time needed to complete the test (Table 1).

Table (1): The degree of minimal hepatic encephalopathy according to NCT.

The degree of encephalopathy	Time of NCT (seconds)
Grade 0 (none)	15-30
Grade 1+ (mild)	31-50
Grade 2+ (moderate)	51-80
Grade 3+ (severe)	81-120
Grade 4+ (coma)	>121

NCT: Number connection test

Baseline vital signs including oxygen saturation, non-invasive blood pressure monitoring, and 5-leads electrocardiogram before, throughout, and post-procedure were recorded.

Intravenous bolus injection of midazolam 1 mg was given with increasing doses every 2–3 minutes till satisfactory sedation was achieved suitable for carrying out the procedure or reaching a total dose of 3 mg. Propofol was started with 1 mg/kg by an anesthesiologist followed by 0.5 mg/kg upon demand every 3 minutes. The patients were sedated by the aforementioned doses aiming to reach a moderate level of sedation where the patient responded appropriately to verbal commands with or without light tactile stimuli. Patients who did not tolerate or the depth of the sedation was increased or even general anesthesia was ensured were excluded from the study.

A record of complications was made for the following events: desaturation <92% on pulse oximetry, a decrease of systolic blood pressure <90 mmHg or heart rate <50 beats/minute, and exacerbation of hepatic encephalopathy diagnosed by increasing the total score of number connection test. UGE was performed using the standard technique. A record was made for the time of the procedure which is the time from giving the sedative drugs till the end of the upper endoscopy.

The degree of alertness and the time for full recovery were recorded. The full recovery was determined by the time when the patients will be oriented to the time, place, and persons and

achieving Aldrete score> 8. Aldrete scoring system is a 5-point scale including, activity, respiration, circulation, consciousness, and oxygen saturation. The patients are assessed on a scale of 0 (worst), 1 (modest), and 2 points in the best condition.

The hemodynamic data, the ability to start oral fluids, the ability to stand up without assistance and pain-free were checked. Any pain encountered was managed using 1 gm of paracetamol intravenously. Patients who received narcotics as 0.5 mg/kg pethidine, were excluded from the study **[11]**.

All patients repeated NCT one hour, before discharge from the endoscopy post-anesthesia care unit (PACU) to ensure the elimination of hypoxemia and antegrade amnesia which could influence the judgment.

After acceptance of all these parameters, the endoscopist discussed the procedure results with the patient and his family members.

Statistical analysis

Statistical Package for Social Science (IBM SPSS) version 23 was used for data analysis. Qualitative data was represented by numbers and percentages. Parametric quantitative data were represented by mean and standard deviations. Non-parametric quantitative data represented by median and inter-quartile range (IQR). The chi-square test compared qualitative data between groups. One-way ANOVA compared parametric quantitative data between groups. Mann-Whitney test compared non-parametric quantitative data. Sensitivity, specificity, positive and negative predictive values were determined. A receiver operating characteristic (ROC) analysis was formed and the best cut-off value for outcome was determined. The confidence interval was 95% and the accepted margin of error was 5%. The P-value was considered significant if it is < 0.05.

RESULTS

Regarding the demographic data of the studied population, the median age with inter-quartile range (IQR) for the studied cases in group A was 46.5 (40.5 –57.5) years old, 48.5 (38.25 – 42.5) years old in group B and 50 (45 – 57) years old in group C. Six of them (60%) were male patients in group A, 24 (80%) in group B and 20 (67%) in group C. The mean value of BMI was 27.8±6 in group A, 27.7±5.4 in group B, and 28.1±3.9 in group C.

The whole number of CLD in the studied population was 60 patients, 40 patients (66.67%) due to HCV, 5 patients (8.3%) due to HBV, 7 patients (11.67%) due to bilharziasis, 3 patients (5.0%) due to Budd-Chiari syndrome, 2 patients (3.3%) due to autoimmune hepatitis and 3 patients (5.0%) of unknown etiology.

The number of cirrhotic patients with abnormal pre-sedation NCT times in the midazolam group was 18 patients (60%), and this number was raised to 25 patients (83.3%) after one hour following sedation with midazolam (P<0.001). The number of cirrhotic patients with abnormal pre-sedation NCT times in the propofol group was 22 patients (73.3%), and this number did not change after one hour following sedation with propofol (P= 0.714).

Regarding NCT before, table (3) showed a significant increase in group C versus group B, while both groups B and C showed a significant increase versus group A.

Regarding NCT one hour later, table (3) showed a significant increase in group B versus group C, while both groups B and C showed a significant increase versus group A.

Regarding the delta change of NCT, table (3) showed a significant increase in group B versus both groups A and C.

Table (3) showed a significantly higher NCT value one hour after than NCT before in group B (P<0.001).

Times of procedure and recovery were significantly increased in group B in comparison to group C [median (IQR): 15 (9.25-20) and 39 (38-40.25) respectively, p<0.001).

A significant decrease in blood pressure associated with a significant increase in pulse and decrease in oxygen saturation was recorded during the procedure in groups B (P<0.001) and C (P<0.004). These changes were improved significantly after the procedure except for blood pressure in group B (P<0.016). Oxygen saturation was significantly decreased in group C versus group B during the procedure with significantly lesser improvement in group C after applying a rebreathing oxygen face mask at a flow of 7 L/min with no need for intubation (Table 4).

Table (2): Laboratory data of cirrhotic patients who received sedation.

Parameter	Group B (n=30)	Group C (n=30)	P-value
Laboratory investigations [mean ± SD]			
Hemoglobin [g/dL, mean ± SD]	10.9±1.99	10.7±1.73	0.746
White blood cells [10^3/uL, median (IQR)]	4.9 (4.1 – 6.3)	4.25 (3.3 – 6.7)	0.28
Platelets [10^3/uL, median (IQR)]	92.5 (70.8– 114.3)	106 (71 –138.5)	0.446
INR [mean ± SD]	1.24±0.27	1.39±0.26	0.022
ALT [IU/L, median (IQR)]	33.5 (21.8– 48.3)	30 (19.8 – 37.3)	0.174
AST [IU/L, median (IQR)]	33 (30 –50.3)	34.5(28.8 – 42.3)	0.554
Total bilirubin [mg/dL, median (IQR)]	1.8 (1.1 – 2.7)	1.95 (1.45–2.78)	0.711
Albumin [g/dL, mean ± SD]	2.99±1.73	2.77±0.68	0.188
AFP [IU/mL, median (IQR)]	5 (2–8)	5.5 (2.35 – 13)	0.491
Serum creatinine [mmol/L, median (IQR)]	0.7 (0.5 – 0.8)	0.9 (0.58 –1.1)	0.038
Blood urea nitrogen [mg/dL, median (IQR)]	15 (12.8 – 20.5)	14 (11.8 –19.8)	0.299
Serum sodium [mmol/L, mean ± SD]	134.5±4.06	131.93±4.18	0.019
Serum potassium [mmol/L, mean ± SD]	3.88±0.48	3.96±0.58	0.545
MELD Score [median (IQR)]	11.22 (10.5– 16.3)	12.8 (10.8 –17)	0.132
Child-Pugh score [n (%)] A B C	 14 (46.7%) 10 (33.3%) 6 (20.0%)	 8 (26.7%) 15 (50.0%) 7 (23.3%)	0.258

AFP, alpha-fetoprotein.; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; SD, standard deviation.

Table (3): Comparison of the number-connection test between studied groups.

	Group A (n=10)	Group B (n=30)	Group C (n=30)	P-value
NCT before [seconds, mean ± SD]	43.6±6.38	59.23±17.8	68.8±20.49	0.003
NCT one hour after [seconds, mean ± SD]	40.5±6.91	79.67±30.13	68.8±19.18	<0.001
ΔNCT [seconds, mean ± SD]	-0.07±0.09	0.33±0.21	0.001±0.07	<0.001

NCT, number connection test; Δ, delta change = [NCT one hour after - NCT before] / [NCT before]

Table (4): Comparison between Groups B and C according to blood pressure, pulse, and oxygen saturation before, during, and after the procedure.

	Group B (n=30)	Group C (n=30)	P-value
Systolic blood pressure [mmHg, mean ± SD]			
Before	116.7±10.4	112.8±11.2	0.167
During	109.2±9.7	108.5±9.4	0.778
After	106.5±10.6	111.8±11.1	0.063
Pulse [beats per minute, mean ± SD]			
Before	83.66±10.6	81.2±1	0.359
During	91.5±11.2	93.6±15.4	0.548
After	85.9±8	83.1±9.4	0.219
Oxygen saturation [%, mean ± SD]			
Before	97.4±1.6	98±1.3	0.116
During	96.4±1.7	94.3±3	0.002
After	97±1.7	97.8±1.2	0.039

SD, standard deviation.

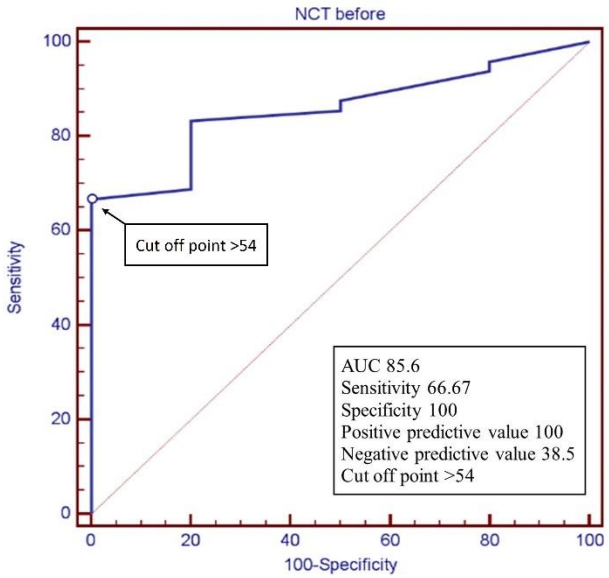

Figure (1): Cut-off point of NCT between control and hepatic patients.

DISCUSSION

Minimal hepatic encephalopathy is indicative of cognitive dysfunction due to cerebral electrophysiological, neurotransmitter, blood flow, metabolism, and fluid homeostatic changes that occur in CLD patients without clinical evidence of hepatic encephalopathy **[12]**.

This study aims to determine the impact of propofol in comparison to midazolam on the occurrence of sub-clinical hepatic encephalopathy in liver cirrhotic patients undergoing UGE.

In this work, we used only the NCT to diagnose MHE because it is easier and has higher validity than other cognitive function tests **[13]** although it was non-specific and could be affected by other factors such as the age of the patient and level of education **[14]**.

We found that most patients with cirrhosis showed evidence of sub-clinical encephalopathy according to the time needed to complete the NCT in comparison to non-hepatic patients before endoscopy similar to another study which reported that 58 patients of cirrhotic patients (95%) had sub-clinical encephalopathy before UGE (NCT: 84.7 ± 77 s; normally less than 30 s) **[15]**.

NCT has been observed to be impaired in the elderly **[16]**, but the age of studied patients included in the present study was <65 years old .

In the present study, we found that in the midazolam group, there is a significant increase of the NCT one hour after endoscopy in comparison to the NCT before the procedure. This means that midazolam in the current study exacerbated subclinical hepatic encephalopathy.

This finding agrees with one study which found that some cirrhotic patients with abnormal NCT showed a statistically significant increase after midazolam intake (pre-sedation 33 patients (54.1%); post-sedation 46 patients (75.4%); p<0.001). Also, it showed that the difference between the mean of pre-sedation (43.5 seconds) and post-sedation (60 seconds) NCT times in cirrhotic patients was statistically significant (p=0.001) **[17]**.

Propofol did not worsen MHE in cirrhotic patients at one hour after sedation when compared to midazolam in agreement with other studies **[18-21]**.

Patients who received propofol took a shorter time for induction of anesthesia and shorter time of procedure and recovered more quickly than patients who received midazolam (p<0.001), so this led to early discharge of the patients after the procedure. This finding comes in agreement with some studies that confirmed that propofol was better than midazolam during recovery from sedation for UGE due to worsening of psychometric tests and critical flicker frequency with midazolam **[21-24]**.

The present study agrees with a meta-analysis result of 12 randomized colonoscopy trials showing significantly lower side effects of propofol including hypoxemia, hypotension, and bradycardia in comparison to benzodiazepines **[25]**.

Also, one study evaluated nurse-administered propofol sedation with the assistance of an anesthesiologist in an endoscopic center of a private hospital in Japan. Among involved patients, 6.7% had hypoxemia (blood oxygen saturation <90%), and 0.62% developed severe hypoxemia (blood oxygen saturation <85%) and required oxygen administration via a nasal cannula, but neither mask ventilation nor endotracheal intubation was needed **[26]**. Also, Wahab et al. reported hypoxia more frequent in the midazolam group, while no hypoxia was recorded in the propofol and combined propofol and midazolam groups **[20]**.

Similar to ours, one study showed hypotension (systolic blood pressure < 90 mm Hg) in 1.2% of upper endoscopy patients and 3.5% of colonoscopy patients after propofol sedation. However, this hypotension was improved immediately after giving an intravenous saline solution **[26]**.

There is still controversy, despite several studies, regarding the unsafety of propofol administration by endoscopists. This assumption was raised by anesthesiologists without any scientific evidence **[26, 27]**.

The limitation of the current study is the usage of only one psychometric test to label patients with MHE, although the used NCT is considered the standard psychometric test .

Future larger studies are needed to determine the clinical relevance of the present study findings on driving and machinery work.

CONCLUSION

The results of the present study clarified that midazolam exacerbates sub-clinical encephalopathy. The hypotension and tachycardia during the procedure were more significant in the midazolam group than in the propofol group. Subjects receiving propofol showed shorter induction, time of procedure, and recovery periods, however for patients' safety, advanced life support should be available when needed.

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Conflict of interest: None.

Ethical consideration

This study was approved by the Research Ethics Committee of the Faculty of Medicine, Ain Shams University following principles of the Declaration of Helsinki (FMASU R75/2022). All studied patients signed for informed and written consent.

HIGHLIGHTS

- Midazolam exacerbates sub-clinical encephalopathy and produces hypotension and tachycardia during upper gastrointestinal endoscopy procedures more than propofol .
- Propofol showed shorter induction, time of procedure, and recovery periods during upper gastrointestinal endoscopy.

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