INTRODUCTION

Hepatic encephalopathy (HE) is a complex neurological disorder associated with advanced liver disease of either acute or chronic nature ***(Ferenci et al., 2002).*** A milder form, referred to as sub-clinical hepatic encephalopathy or minimal hepatic encephalopathy(MHE), is defined as a condition in which patients demonstrate quantifiable neuropsychological defects, yet appear to have a normal mental and neurological status on clinical examination ***(Amodio et al., 2004).*** These patients can work, operate machinery, and drive a car, yet may be at increased risk of injury ***(Kircheis et al., 2009).***

Upper GI endoscopy is routinely performed in patients with chronic liver disease to screen for complications related to portal hypertension such as esophageal and gastric varices and portal gastropathy ***(Toubia and Sanyal 2008).*** Sedation is frequently administered to facilitate patient's tolerance ***(Thuluvath, 2009).***

Patients with hepatic dysfunction, who undergo endoscopy, are at increased risk for complications related to sedation. There are few studies quantifying the risk in this population ***(McGuire, 2011).*** Since most drugs are metabolized in the liver, the choice of endoscopic sedatives may place cirrhotic patients at risk for either enhanced effects of the medication due to higher plasma level or prolonged effects due to delayed clearance ***(Delcò et al., 2005).***

The standard medications, meperidine and benzodiazepines are predominantly metabolized in the liver and cirrhosis impairs first pass clearance as well as metabolism ***(Neal et al., 1979).*** The lower plasma levels of albumin may also decrease drug binding, leading to an increase of its absorption in the tissues, prolonging clearance and thus exacerbating sub-clinical hepatic encephalopathy ***(Steiner et al., 2004).***

Midazolam is a benzodiazepine depressant of the central nervous system that is commonly used for conscious sedation in the general population undergoing upper GIE ***(Keefe, 1995).*** It is widely used because of its short-acting sedative (half-life less than 6h for midazolam), anxiolytic and amnesic properties ***(Tegeder et al., 1999).*** A major component of the half-life is the production of active metabolites that may have different half-lives. However, for midazolam, the initial metabolite, alpha-hydroxyl-midazolam, has a short half-life as well ***(Boulieu et al., 1998).*** Thus, liver patients are at potentially greater risk for complications, including cardiopulmonary compromise, and possible precipitation nor exacerbation of encephalopathy, including subclinical encephalopathy ***(McGuire, 2011).***

Propofol is a short-acting anesthetic agent that can be successfully used as a sedative drug during GI endoscopy. It is rapidly metabolized in the liver by conjugation with glucoronic acid (phase 2 reaction) ***(Mackenzie and Grant, 1987).*** It has a favorable pharmacokinetic profile in comparison to the benzodiazepines and opioids with regard to rapid induction of

sedation, faster recovery, and equivalent levels of amnesia ***(Servin et al., 1990).***

The depth of sedation produced is typically greater than with traditional sedatives used in the outpatient setting. Although propofol undergoes hepatic metabolism, no adjustments in dosage are required in patients with chronic liver disease ***(Servin et al., 1990).*** It has been used effectively and safely in a small study of cirrhotic patients who exhibited significantly shorter induction and recovery periods ***(Weston et al., 2003).*** It was safe even in elderly individuals and in those with multiple co-morbid conditions ***(Kerker et al., 2010).***

In this study, we have investigated the effects of propofol compared to midazolam on the degree of sub-clinical hepatic encephalopathy by using NCT and mean time to achieve full recovery in patients with liver disease who are undergoing upper GIE.

AIM OF THE WORK

The aim of this study is to determine the effects of propofol compared to midazolam on the degree of sub-clinical hepatic encephalopathy in patients with liver cirrhosis who are undergoing upper GI endoscopy.

HEPATIC ENCEPHALOPATHY

Definition:

Hepatic encephalopathy is a major complication of acute and chronic liver disease. This neuropsychiatric syndrome presents clinically with abnormalities in mental status and neuromotor function. Symptoms exist on a spectrum ranging from subtle deficits in attentiveness to severe confusion and even coma ***(Caruana and Shah 2011).***

Hepatic encephalopathy is characterized by personality changes, intellectual impairment, and a depressed level of consciousness. An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through portosystemic collateral vessels ***(Riggio et al., 2005).***

Hepatic encephalopathy is also described in patients without cirrhosis with either spontaneous or surgically created portosystemic shunts. The development of hepatic encephalopathy is explained, to some extent, by the effect of neurotoxic substances, which occurs in the setting of cirrhosis and portal hypertension ***(Ferenci et al., 2003).*** Subtle signs of hepatic encephalopathy are observed in nearly 80% of patients with cirrhosis ***(Bajaj, 2008).***

Symptoms may be debilitating in a significant number of patients and are observed in 24-53% of patients who undergo portosystemic shunt surgery. Approximately 30% of patients dying

of end-stage liver disease experience significant encephalopathy, approaching coma ***(Ferenci et al., 2003).***

Hepatic encephalopathy, accompanying the acute onset of severe hepatic synthetic dysfunction, is the hallmark of fulminant hepatic failure (FHF). Symptoms of encephalopathy in FHF are graded using the same scale used to assess encephalopathy symptoms in cirrhosis ***(Ferenci et al., 2002).***

The encephalopathy of cirrhosis and FHF share many of the same pathogenic mechanisms. However, brain edema plays a much more prominent role in FHF than in cirrhosis. The brain edema of FHF is attributed to increased permeability of the blood-brain barrier, impaired osmoregulation within the brain, and increased cerebral blood flow. The resulting brain cell swelling and brain edema are potentially fatal. In contrast, brain edema is rarely reported in patients with cirrhosis ***(Ferenci et al., 2002).***

Types:

A classification of hepatic encephalopathy was introduced at the World Congress of Gastroenterology 1998 in Vienna. According to this classification, hepatic encephalopathy is subdivided in type A, B and C depending on the underlying cause ***(Ferenci et al., 2002).***

- *Type A (=acute)*: Describes hepatic encephalopathy associated with acute liver failure, typically associated with cerebral edema.

- *Type B (=bypass)*: Is caused by portal-systemic shunting without associated intrinsic liver disease.
- *Type C (=cirrhosis*): Occurs in patients with cirrhosis - this type is subdivided in episodic, persistent and minimal encephalopathy.

The term minimal hepatic encephalopathy (MHE) is defined as encephalopathy that does not lead to clinically overt cognitive dysfunction, but can be demonstrated with neuropsychological studies ***(Randolph et al., 2009).***

This is still an important finding, as minimal encephalopathy has been demonstrated to impair quality of life and increase the risk of involvement in road traffic accidents ***(Bajaj, 2010).***

Epidemiology and prognosis:

In those with cirrhosis, the risk of developing hepatic encephalopathy is 20% per year, and at any time about 30–45% of people with cirrhosis exhibit evidence of overt encephalopathy. The prevalence of minimal hepatic encephalopathy detectable on formal neuropsychological testing is 60–80%; this increases the likelihood of developing overt encephalopathy in the future ***(Bajaj, 2010).***

Once hepatic encephalopathy has developed, the prognosis is determined largely by other markers of liver failure, such as the levels of albumin, the prothrombin time, the presence of ascites

and the level of bilirubin. Together with the severity of encephalopathy, these markers have been incorporated into the Child-Pugh score; this score determines the one- and two-year survival and may assist in a decision to offer liver transplantation ***(Ferenci et al., 2002).***

The Child-Pugh score (Pugh, et al., 1973)

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

Table (1): The Child-Pugh score classification

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/l	>35	28-35	<28
PT INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Interpretation

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

In acute liver failure, the development of severe encephalopathy strongly predicts short-term mortality, and is almost as important as the nature of the underlying cause of the liver failure in determining the prognosis ***(Polson et al., 2005).***

The occurrence of hepatic encephalopathy in patients with Wilson's disease (hereditary copper accumulation) and mushroom poisoning indicates an urgent need for a liver transplant ***(Polson et al., 2005).***

Pathogenesis:

A number of theories have been proposed to explain the development of hepatic encephalopathy in patients with cirrhosis. Some investigators contend that hepatic encephalopathy is a disorder of astrocyte function ***(Brusilow, 2002).***

Astrocytes account for about one third of cortical volume. They play a key role in the regulation of the blood-brain barrier. They are involved in maintaining electrolyte homeostasis and in providing nutrients and neurotransmitter precursors to neurons. They also play a role in the detoxification of a number of chemicals, including ammonia ***(Brusilow, 2002).***

It is theorized that neurotoxic substances, including ammonia and manganese, may gain entry into the brain in the setting of liver failure. These neurotoxic substances may then contribute to morphologic changes in astrocyte ***(Caruana and Shah, 2011).***

In cirrhosis, Astrocytes may undergo Alzheimer type II astrocytosis. Astrocytes exposed to ammonia for prolonged periods can undergo a morphologic change to Alzheimer's type 2 astrocyte characterized by large nuclei, prominent nucleoli, and marginated chromatin ***(Seyan et al., 2010).***

Prolonged exposure to ammonia can also cause a shift in the balance of neurotransmission to result in overall inhibition of post-synaptic potentials. This neuroinhibitory state is characteristic of the hepatic encephalopathy seen in patients with chronic liver disease. Accumulated glutamine acts as an osmolyte within astrocyte, causing cellular swelling and low-grade cerebral edema disturbing the cerebral oscillatory networks ***(Prakash and Mullen, 2010).***

The changes of Alzheimer type II astrocytosis are not seen in FHF. But, in contrast to cirrhosis, astrocyte swelling in FHF may be so marked as to produce brain edema. This may lead to increased intracranial pressure and potentially brain herniation ***(Caruana and Shah, 2011).***

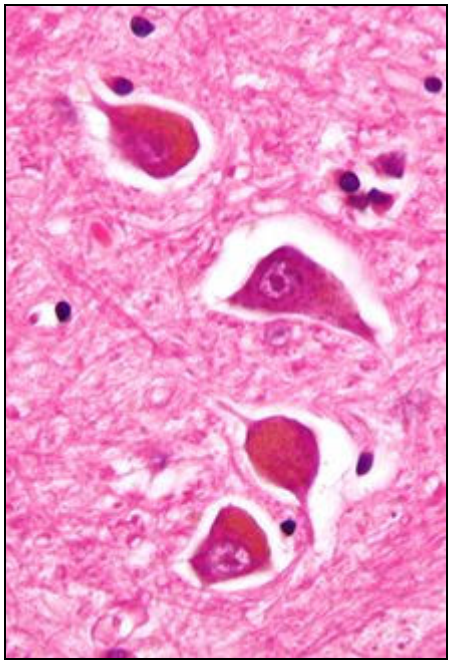

Figure (1): Micrograph of Alzheimer type II astrocyte, as may be seen in hepatic encephalopathy ***(Seyan et al., 2010).***

Patients with worsening encephalopathy should undergo head CT scan to rule out the possibility of an intracranial lesion, including hemorrhage. Certainly, cerebral edema, if discovered, should be aggressively managed. The true incidence of elevated intra-cranial pressure (ICP) in patients with cirrhosis and severe hepatic encephalopathy remains to be determined ***(Caruana and Shah 2011).***

Work focused on changes in gene expression in the brain has been conducted. The genes coding for a wide array of transport proteins may be up regulated or down regulated in cirrhosis and FHF. As an example, the gene coding for the peripheral-type benzodiazepine receptor is up regulated in both cirrhosis and FHF. Such alterations in gene expression may ultimately result in impaired neurotransmission ***(Butterworth, 2003).***

Hepatic encephalopathy may also be thought of as a disorder that is the end result of accumulated neurotoxic substances in the brain. Putative neurotoxins include short-chain fatty acids; mercaptans; false neurotransmitters, such as tyramine, octopamine, and beta-phenylethanol amines; manganese; ammonia; and gamma-amino butyric acid (GABA) ***(Caruana and Shah, 2011).***

1. Ammonia hypothesis:

In humans, the colon is a major site of ammonia production. Ammonia is a product of intestinal bacterial metabolism of protein and other nitrogenous compounds. Intestinal enterocytes also contribute to ammonia production through the utilization of glutamine ***(Mullen, 2010).***

In healthy individuals, ammonia is converted to urea in the liver, which is then excreted by the kidneys. In patients with liver failure or portosystemic shunting, ammonia bypasses liver

metabolism and accumulates in systemic circulation ***(Prakash and Mullen, 2010).***

This ammonia then undergoes metabolism at extra hepatic sites such as skeletal muscle and brain tissue. In the central nervous system, Astrocytes are the glial cells that provide nutrients, maintain extracellular ion balance, and express the enzyme glutamine synthetase which converts ammonia to glutamine ***(Prakash and Mullen, 2010).***

Exposure of Astrocytes to toxic levels of ammonia and subsequent accumulation of glutamine causes changes that may explain the neuronal dysfunction seen in hepatic encephalopathy ***(Seyan et al., 2010).***

Prolonged exposure to ammonia can also cause a shift in the balance of neurotransmission to result in overall inhibition of post-synaptic potentials. This neuroinhibitory state is characteristic of the hepatic encephalopathy seen in patients with chronic liver disease ***(Prakash and Mullen, 2010).***

Accumulated glutamine acts as an osmolyte within Astrocytes, causing cellular swelling and low-grade cerebral edema disturbing the cerebral oscillatory networks ***(Prakash and Mullen, 2010).***

Glutamine also increases the oxidative stress within Astrocytes causing protein and RNA modifications which impact

synaptic plasticity and glioneuronal communication ***(Haussinger and Schliess, 2008).***

Researchers are currently trying to define how other factors such as inflammation, infection, hyponatremia, and sedative/ narcotic use may work synergistically with ammonia to promote astrocyte changes and symptom progression ***(Caruana and Shah, 2011).***

Ammonia is produced in the gastrointestinal tract by bacterial degradation of amines, amino acids, purines, and urea. Enterocytes also convert glutamine to glutamate and ammonia by the activity of glutaminase ***(Butterworth and Chatauretn, 2004).***

Two factors contribute to the hyperammonemia that is seen in cirrhosis. *First*, there is a decreased mass of functioning hepatocytes, resulting in fewer opportunities for ammonia to be detoxified by the above processes. *Secondly*, portosystemic shunting may divert ammonia-containing blood away from the liver to the systemic circulation ***(Butterworth and Chatauretn, 2004).***

2. *GABA hypothesis:*

GABA is a neuroinhibitory substance produced in the gastrointestinal tract. Of all brain nerve endings, 24-45% may be GABAergic. For 20 years, it was postulated that hepatic encephalopathy was the result of increased GABAergic tone in the brain ***(Schafer, 1982).***

However, experimental work is changing perceptions regarding the activity of the GABA receptor complex in cirrhosis ***(Ahboucha et al., 2004).***

The GABA receptor complex contains binding sites for GABA, benzodiazepines, and barbiturates. It was believed that there were increased levels of GABA and endogenous benzodiazepines in plasma. These chemicals would then cross an extra permeable blood-brain barrier. Binding of GABA and benzodiazepines to a supersensitive neuronal GABA receptor complex permitted the influx of chloride ions into the postsynaptic neuron, leading to generation of an inhibitory postsynaptic potential ***(Ahboucha et al., 2004).***

However, experimental work has demonstrated that there is no change in brain GABA or benzodiazepine levels. Similarly, there is no change in sensitivity of the receptors of the GABA receptor complex ***(Ahboucha et al., 2004).***

Previously, it was believed that administration of flumazenil, a benzodiazepine receptor antagonist, could improve mental function in patients with hepatic encephalopathy. It now appears that flumazenil improves mental function in only a small percentage of patients with cirrhosis. Neurotoxins, like ammonia and manganese, increase the production of the peripheral-type benzodiazepine receptor (PTBR) in Astrocytes ***(Butterworth, 2000).***