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THE CLINICAL EFFECTS OF NITAZOXANIDE IN HEPATIC ENCEPHALOPATHY PATIENTS: A PILOT STUDY

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ABSTRACT: Background: Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting. It is associated with poor survival and high risk of recurrence along with reduced quality of life (QOL) of patients and their caregivers. Nitazoxanide (NTZ) is an oral antimicrobial that improved mental status and QOL score in HE patients and is well-tolerated. **Aim:** To evaluate the efficacy and safety of NTZ compared to metronidazole and rifaximin in patients with grade II-III HE and to evaluate its effect on patients' QOL. **Patients and Methods:** A Prospective, Randomized, Controlled, Open-Label, Pilot study. Thirty four patients were randomly assigned to receive either Nitazoxanide (n=12), Metronidazole (n=11) or Rifaximin (n=11) for 7 days. Serum ammonia level, Clinical Hepatic Encephalopathy Staging Scale (CHESS) and Chronic Liver Disease Questionnaire (CLDQ) for QOL was measured at baseline and at end of treatment. **Results:** Baseline and after 1 week serum ammonia levels and CHESS scores, showed no significant difference among the 3 groups. There was no significant difference in serum ammonia level in each group for the 3 groups while it showed significance in CHESS score. Regarding QOL, there was a significant difference between baseline and after 1 week CLDQ total (p-value= 0.01) and fatigue scores (p-value= 0.01) for Nitazoxanide group. **Conclusion:** Administration of 500 mg of NTZ twice daily over 7 days showed the same efficacy on HE as standard treatment. However, it was superior in improving patients' QOL.

INTRODUCTION: Hepatic encephalopathy has been defined as "a brain dysfunction caused by liver insufficiency and/or portosystemic shunting;" [1]. It ranges from minimal hepatic encephalopathy (MHE) "a condition in which patients with cirrhosis exhibit various quantifiable neuropsychological defects using certain psychometric tests", to overt HE showing multiple neuropsychiatric problems with the risk of cerebral edema and death [2, 3].

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Overt HE occurs in approximately 30–45% of patients with cirrhosis and 10–50% of patients with transjugular intrahepatic portosystemic shunt [4], while MHE is estimated to have a prevalence ranging from 22% to 80% [5].

Several mechanisms have been proposed to explain the pathogenesis of HE where ammonia theory enjoys maximum attention. Hyperammonemia interferes with glutamatergic and serotonergic transmission and increases production and accumulation of glutamine in astrocytes that leads to increased osmotic pressure and edema [6, 7]. Thus, most therapies for HE are focused on lowering serum ammonia level [8].

HE is associated with poor survival and high risk of recurrence [9, 10]. Even in its mildest form, HE

reduces health-related QOL of patients and their caregivers [11, 12]. Cognitive impairment associated with cirrhosis results in utilization of more health care resources in adults [13].

The current standard of care for patients with HE includes non-absorbable disaccharides (lactulose) [14], and non-absorbable antibiotics (neomycin, vancomycin, rifaximin and metronidazole) [15]. Because of the systemic absorption of these antimicrobial agents (except for rifaximin), serious adverse effects have been recorded, and these have limited their widespread use.

Nitazoxanide is an oral antimicrobial that showed activity against various protozoa, helminthes, viruses and anerobic bacteria. It inhibits an early step of the pyruvate: ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction, through blocking the formation of CO2 and acetyl-CoA, and the transfer of reducing equivalents to redox-active dyes [16].

Nitazoxanide is the first drug approved for the treatment of Cryptosporidium infection [17-19]. It was also effective in treating *Giardia lamblia* [20], *Blastocystis hominis* [21], amoebiasis [22], *Ascaris lumbricoides* [23], *Taenia saginata* [24], *Fasciola hepatica* [25], *Trichurius trichiura* [26], *Clostridium difficile* [27], *and Helicobacter pylori* [28].

Basu and colleagues presented a pilot prospective study showing clinical improvement in HE among cirrhotic patients who received NTZ and lactulose. Patients showed improvement in mental status and QOL score, and the drug was well-tolerated [29].

The aim of this study was to evaluate the efficacy and safety of NTZ compared to metronidazole and rifaximin inpatients with grade II-III HE and to evaluate its effect on the improvement of patients' QOL.

Patients and methods:

The current study was Prospective, Randomized, Controlled, Open-Label, Pilot study, conducted on 34 Egyptian adult in patients with HE. The study was conducted at Tropical Medicine Department, Ain Shams University Hospitals and Al-Azhar University Hospitals, Cairo, Egypt. The study protocol was revised and approved by the research ethics committee at Faculty of Pharmacy, Ain shams University. Prior to participation all eligible patients' caregivers were educated about the study protocol and signed the written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients:

Inclusion criteria comprised: Adult Patients from 18 to 65 years with grade II-III HE. Patients were excluded from the study if they had; active GIT bleeding, major psychiatric illness, renal insufficiency (serum creatinine > 2 mg/dl) ,compromised biliary functions, AIDS or hypersensitivity to NTZ, had been receiving medications highly bound to plasma proteins (eg. warfarin), benzodiazepines, narcotics, alcohol and marijuana, or pregnant or lactating women.

Methods:

The study includes a total of 34 patients that were randomly assigned by simple randomization to one of 3 groups: Nitazoxanide group (12 patients who received 500 mg NTZ tablets twice daily for seven days), Metronidazole group (11 patients who received 250 mg metronidazole tablets every 8 hours for seven days) and Rifaximin group (11 patients who received 200 mg rifaximin tablets every 8 hours for seven days). All patients received 30 – 60 ml oral lactulose three times a day for seven days, so that patient passes two to three semisoft stools in a day.

At baseline, all patients underwent thorough history taking and clinical examination. Liver disease staging was performed using Model for End stage Liver Disease (MELD) score [30], and blood samples were collected to evaluate serum sodium, potassium, total bilirubin, albumin, creatinine, INR, prothrombin time (PT), hemoglobin level, WBC count and platelet count.

The following parameters were measured at baseline and at end of treatment and used to evaluate the treatment outcomes : serum ammonia level, severity of hepatic encephalopathy using Clinical Hepatic Encephalopathy Staging Scale (CHESS) [31], and QOL using Chronic Liver Disease Questionnaire (CLDQ) [32]. Serum ammonia was

measured spectrophotometrically using commercial kit [33].

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 21. All p-values are two-sided. P-values < 0.05 were considered significant.

RESULTS:

From November 2012 to December 2014 a total of 80 patients were assessed for eligibility and only 60 cirrhotic patients fulfilled the inclusion criteria and were included in the study. However, Out of the 60 patients, only 34 completed the study. Twenty six patients were dropped out due to their desire to leave the hospital within the first few days from their recruitment. Hence, per protocol statistical analysis was done.

Baseline evaluation:

Fourteen females (41.2%) and twenty males (58.8%) were enrolled and distributed in the 3 groups as follows: 6 (50%) male and 6 (50%) female patients in Nitazoxanide group, 7 (63.6%) male and 4 (36.4%) female patients in Metronidazole group, while 7 (63.6%) male and 4 (36.4%) female patients in Rifaximin group. The median age of the patients was 55 years. All the patients were presented with HCV as their cause of cirrhosis except 1 patient with HBV and 1 patient with Wilson's disease in Rifaximin group.

There was no significant difference among the 3 groups regarding age and MELD score (p-value > 0.05) and no statistical analysis was done for the causes of HE as the numbers were too small for a valid statistical analysis **(Table 1)**.

There was no significant difference among the 3 groups regarding baseline laboratory parameters (p-value > 0.05). However, Nitazoxanide group had significantly higher levels of serum albumin than Rifaximin group (p-value= 0.018). While Metronidazole group showed significantly lower levels of platelet count than the other 2 groups (p-value= 0.001) **(Table 2)**.

For HE related parameters, there was no significant difference among the 3 groups regarding serum ammonia level and CHESS score. While no statistical analysis was done for HE grade as numbers were too small for valid statistical analysis **(Table 3)**.

TABLE 1: BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Parameter	Nitazoxanide gp	Metronidazole gp	Rifaximin gp	p-value
Age	56.5 (51.3-61.5)	56 (40-58)	55 (45-60)	0.519
MELD score	14.5 (11.5-21)	19 (15.5-21)	16.5 (12.8-24.5)	0.480
Cause of HE:*				
High protein diet	4 (33.3%)	2 (18.2%)	5 (45.5%)	
Constipation	2 (16.7%)	1 (9.1%)	4 (36.4%)	
Dehydration	1 (8.3%)	0 (0%)	2 (18.2%)	
Infection	5 (41.7%)	3 (27.3%)	0 (0%)	
Unknown	3 (25%)	4 (36.4%)	2 (18.2%)	

Data are expressed as medians (inter quartile range) and numbers (%).

Baseline Inter-group comparisons among the 3 groups were non-significant (p-value >0.05) and calculated using Kruskal-Wallis test.

* No statistical analysis was done as numbers were too small for valid statistical analysis

TABLE 2: BASELINE LABORATORY PARAMETERS

Parameter	Nitazoxanide gp	Metronidazole gp	Rifaximin gp	p-value
Serum sodium (mmol/L)	128 (124.8-135.1)	132 (124.7-136)	135 (121-139)	0.864
Serum potassium (mmol/L)	4.05 (3.6-4.5)	4 (3.4-4.4)	3.05 (3.2-3.6)	0.185
Serum total bilirubin (mg/dl)	2.01 (1.4-3)	3.16 (2-5.3)	1.95 (1.4-15.9)	0.400
INR	1.65 (1.1-1.8)	1.8 (1.8-2.2)	1.7 (1.5-2)	0.052
PT (seconds)	16.45 (13.2-18.5)	18 (14-20)	17.1 (16-19)	0.355
Serum albumin (g/dl)	2.6 (2.3-2.8)	2.1 (1.7-2.4)	2.1 (1.6-2.2)	0.018*
Serum creatinine				

(mg/dl)	1.18 (0.9-1.4)	0.96 (0.7-1.1)	1.05 (0.7-1.2)	0.355
WBC count (10^3/mm^3)	7.55 (5.3-10.4)	5.3 (3.9-6.8)	7.5 (5.1-11.6)	0.080
Hb level (g/dl)	11.55 (11.1-11.9)	10.9 (9.8-11.9)	8.7 (8-12.3)	0.071
Platelet count (10^3/mm^3)	110.5 (70.5-155)	54 (37-83)	113 (99-152)	0.001*

Data are expressed as medians (inter quartile range).

Baseline Inter-group comparisons among the 3 groups were non-significant (p-value >0.05) except for serum albumin and platelet count. P-value was calculated using Kruskal-Wallis test. * Multiple pair-wise comparisons were done using the Bon-Ferroni adjustment test.

TABLE 3: HEPATIC ENCEPHALOPATHY RELATED PARAMETERS

Parameter	Nitazoxanide gp	Metronidazole gp	Rifaximin gp	p-value
HE grade:*				
Grade II	6 (50%)	5 (45.5%)	4 (36.4%)	
Grade III	6 (50%)	6 (54.5%)	7 (63.6%)	
Serum ammonia levels (µg/dl)	198.55 (142.7-270.9)	177 (142-321.6)	145 (112-165)	0.083
CHESS scores	7.5 (4.3-9)	7 (6-8)	7 (5-7)	0.792

Data are expressed as medians (inter quartile range) and numbers (%).

Baseline Inter-group comparisons among the 3 groups were non-significant (p-value >0.05) and calculated using Kruskal-Wallis test.

* No statistical analysis was done for HE grade as numbers were too small for valid statistical analysis.

Clinical outcomes evaluation:

I- Efficacy:

Baseline and after 1 week ammonia levels for the 3 groups showed no significant difference (p-value >0.05). Moreover, the comparison between baseline and after 1 week ammonia level showed no significant difference among the 3 groups (p-value >0.05) **(Table 4) (Fig.1)**.

The study groups were also compared for CHESS score at baseline and after 1 week and showed no significant difference (p-value >0.05). However, there was a significant difference between baseline CHESS score and CHESS score after 1 week among each group where Nitazoxanide showed the greatest significance (p-value= 0.01) **(Table 4) (Fig. 2)**.

TABLE 4: COMPARISON OF SERUM AMMONIA LEVELS AND CHESS SCORES AT BASELINE AND AFTER 1 WEEK AMONG THE STUDY GROUPS

Parameter	Nitazoxanide gp	Metronidazole gp	Rifaximin gp	p-value[a]
Serum ammonia level at baseline (µg/dl)	198.55 (142.7-270.9)	177 (142-321.6)	145 (112-165)	0.083
Serum ammonia level after 1 week (µg/dl)	188.85 (72.4-272)	170 (106.9-230)	167 (110-221)	0.984
p-value[b]	0.182	0.114	0.424	
CHESS score at baseline	7.5 (4.3-9)	7 (6-8)	7 (5-7)	0.792
CHESS score after 1 week	0 (0-0)	0 (0-0)	0 (0-2)	0.744
p-value[b]	0.01	0.025	0.015	

Data are expressed as medians (inter quartile range).

[b] Intra-group comparisons (Baseline vs. 1 week) were calculated using Wilcoxon signed rank test and were significant for CHESS score, p-value > 0.05: non-significant.

[a] Inter-group comparisons (Baseline and 1 week) among the 3 groups were non-significant (p-value >0.05) and calculated using Kruskal-Wallis test.

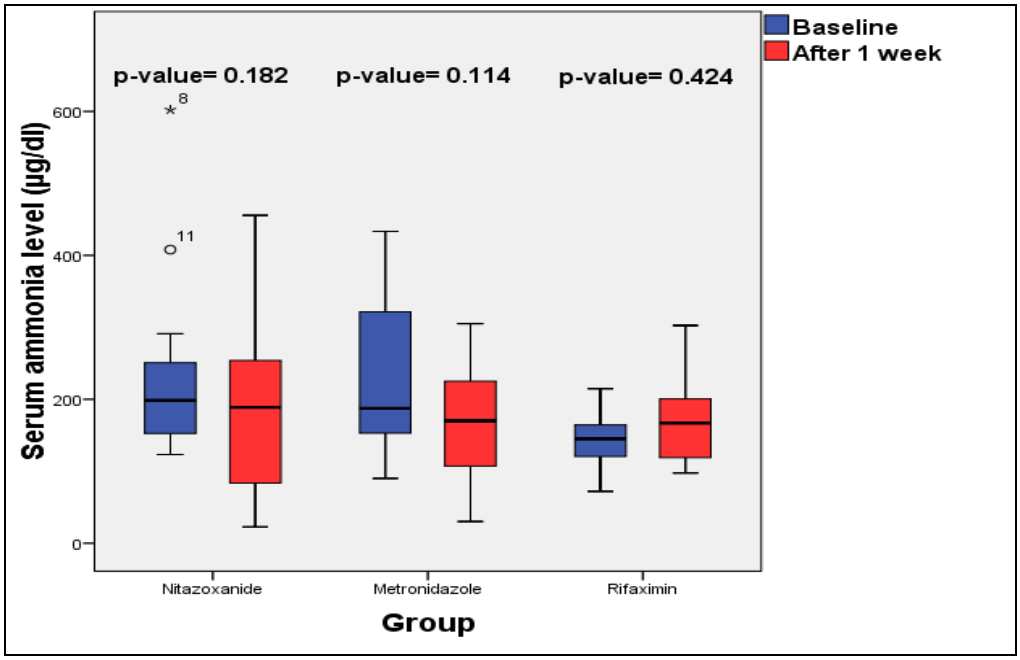

FIG.1: SERUM AMMONIA LEVELS AT BASELINE AND AFTER 1 WEEK FOR THE STUDY GROUPS.

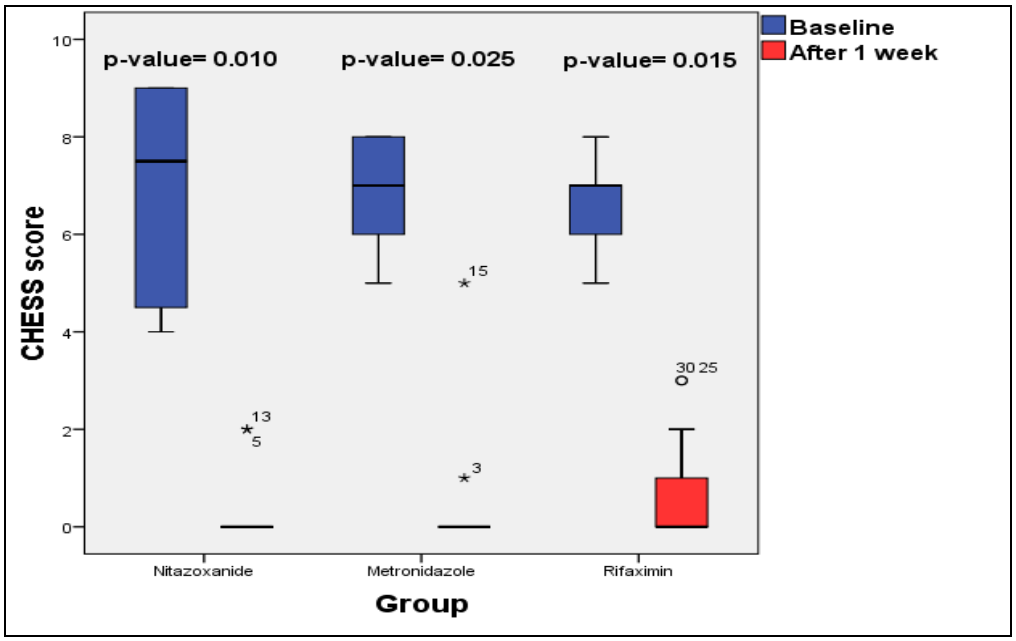

FIG.2: CHESS SCORES AT BASELINE AND AFTER 1 WEEK FOR THE STUDY GROUPS.

II- Safety:

Out of 34 patients enrolled in the study, 17 patients did not show any adverse events throughout the study including 6 (17.6%) patients from Nitazoxanide group, 5 (14.7%) patients from Metronidazole group, and 6 (17.6%) patients from Rifaximin group. The adverse events consisted of constipation (2 Nitazoxanide, 1 Metronidazole), diarrhea (2 Nitazoxanide, 3 Metronidazole), dry mouth (3 Nitazoxanide, 1 Metronidazole), vomiting (1 Nitazoxanide, 1 Metronidazole, 1 Rifaximin), nausea (1 Metronidazole), anorexia (1 Metronidazole and 2 Rifaximin), fever (1 Metronidazole and 2 Rifaximin), rash (1 Nitazoxanide), dizziness (1 Nitazoxanide and 1 Rifaximin), headache (1 Nitazoxanide), dysuria (1 Metronidazole), tremors (1 Nitazoxanide and 1 Rifaximin) and epistaxis (1 Nitazoxanide). Four patients died during the follow up period after the intervention week, 1 (8.3%) patient in Nitazoxanide group, 1 (9.1%) patient in Metronidazole group and 2 (18.2%) patients in Rifaximin group.

No statistical analysis was done as the numbers were too small for a valid statistical analysis.

III- Quality of life:

Baseline and after 1 week CLDQ total and domain scores among the 3 groups showed no significant difference (p-value >0.05). However, post hoc test showed that Rifaximin group had significantly lower activity score than the other 2 groups at baseline (p-value= 0.011) while Metronidazole group had significantly higher fatigue score than that of Rifaximin group after 1 week (p-value= 0.042).

Moreover, there was a significant difference between baseline and after 1 week CLDQ total score (p-value= 0.01) and fatigue score (p-value= 0.01) for Nitazoxanide group **(Fig. 3)**, while the other two groups showed no significant difference. The other domains showed no significant difference between baseline and after 1 week scores for the 3 groups (p-value >0.05) **(Table 5)**.

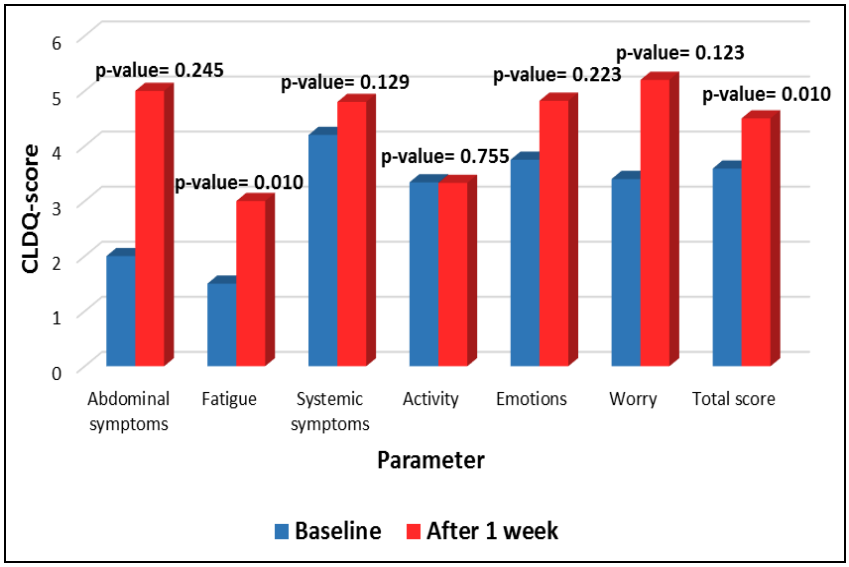

FIG.3: CLDQ TOTAL AND DOMAIN SCORES FOR NITAZOXANIDE GROUP AT BASELINE AND AFTER 1 WEEK.

TABLE 5: COMPARISON OF CLDQ TOTAL AND DOMAIN SCORES AT BASELINE AND AFTER 1 WEEK AMONG THE STUDY GROUPS

Parameter	Nitazoxanide gp	Metronidazole gp	Rifaximin gp	p-value[a]
Abdominal symptoms				
Baseline	2 (1-4.8)	4 (1-7)	1 (1-1)	0.076
After 1 week	5 (2.5-6.7)	7 (3-7)	1 (1-7)	0.428
p-value[b]	0.245	0.141	0.059	
Fatigue				
Baseline	1.5 (1-3.1)	2.6 (1.4-4.6)	1.4 (1.2-3.4)	0.193
After 1 week	3 (2.3-5.6)	5.6 (3.8-6.6)	2.4 (1.4-4.4)	0.042*
p-value[b]	0.01	0.18	0.342	
Systemic symptoms				
Baseline	4.2 (3.1-5.2)	3.8 (2.6-5.4)	3.8 (2-4.4)	0.689
After 1 week	4.8 (4.1-5.6)	4.8 (4-6.8)	4.2 (3.6-5.6)	0.562
p-value[b]	0.129	0.074	0.058	
Activity				
Baseline	3.34 (1.6-5)	3 (2.3-3.7)	1.67 (1-2.3)	0.011*
After 1 week	3.33 (2-4.4)	3 (1.7-5.7)	3 (1-4)	0.673
p-value[b]	0.755	0.284	0.065	
Emotional function				
Baseline	3.75 (2.9-5.7)	3.88 (3-5.8)	4.88 (2.6-5.5)	0.937
After 1 week	4.82 (3.5-6.4)	4 (4-6)	5.13 (3.4-6.4)	0.990

p-value[b]	0.223	0.373	0.374	
Worry				
Baseline	3.4 (2.2-6.8)	4.6 (2.2-7)	5.4 (3.8-7)	0.413
After 1 week	5.2 (2.4-7)	5 (3.8-7)	5.4 (4.2-7)	0.807
p-value[b]	0.123	0.593	0.833	
Total score				
Baseline	3.59 (2.8-4.3)	3.86 (3.1-4.6)	3.62 (2.7-4)	0.238
After 1 week	4.5 (3.6-5.4)	4.86 (3.9-5.9)	4.45 (3.1-5.2)	0.413
p-value[b]	0.01	0.062	0.205	

Data are expressed as medians (inter quartile range).

[b] Intra-group comparisons (Baseline vs. 1 week) were non-significant (p-value >0.05), except for total and fatigue scores in Nitazoxanide group, and calculated using Wilcoxon signed rank test.

[a] Inter-group comparisons (Baseline and 1 week) among the 3 groups were non-significant (p-value >0.05), except for activity score at baseline and fatigue score after 1 week, and calculated using Kruskal-Wallis test.

* Multiple pair-wise comparisons were done using the Bon-Ferroni adjustment test.

DISCUSSION: Several mechanisms have been proposed to explain the pathogenesis of HE such as increased deposition of cerebral manganese [34], neurostreoids pathway activation [35], and involvement of infection, systemic inflammation and oxidative stress in HE pathogenesis [36-38]. However, there is a consensus that an excessive accumulation of ammonia in brain is the primary causative factor of HE [39]. Thus the mainstay treatment for HE revolves about reducing the production and absorption of ammonia in the gut, and to improve its excretion by drug therapy or diet modification. Currently, lactulose and nonabsorbable antibiotics are the most commonly used therapeutics to treat HE [40].

Traditionally, nonabsorbable disaccharides have been used as the first-line therapy for patients with HE [1], even if their effectiveness in comparison with placebo has not been proven [41].

Antibiotics are regarded as a therapeutic alternative to nonabsorbable disaccharides for HE [42]. Neomycin is a non-absorbable aminoglycoside that has also been prescribed for HE, but its ototoxicity and nephrotoxicity limit its use [43]. Metronidazole also improves HE, however its potentially severe neurotoxicity in patients with cirrhosis has been documented with long-term administration and limits its common use [44]. Vancomycin, has been demonstrated to lower blood ammonia and attenuated HE in patients with cirrhosis. However, its use has led to bacterial overgrowth and increased the risk of enteric bacterial resistance [45].

Rifaximin is considered as second-line in patients who fail disaccharide therapy and as first-line in those intolerant of disaccharides. It has a beneficial effect on HE and may reduce mortality and has the advantage of being well tolerated with minimal risk of causing bacterial resistance [46]. However, some studies showed that rifaximin was not superior to non-absorbable disaccharides for either HE treatment or prevention, with a similar incidence of side-effects [47]. Two case studies described an association between Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN) and rifaximin [48, 49]. Moreover, *Clostridium difficile* colitis has been observed and *Candida albicans* has been isolated in two studies. In addition, selection of resistant mutants of both Gram-negative and -positive bacteria in the gastrointestinal tract cannot be definitely ruled out [50, 51]. Electrolyte alterations (sodium and potassium) have been reported during rifaximin therapy, a warning for its long-term use in cirrhotics [50]. It also has higher per-treatment-cost than non-absorbable disaccharides [52].

Nitazoxanide is a new thiazolide antiparasitic agent that specifically targets anaerobes in the intestinal tract beside other protozoa and helminthes. It is given by oral route with good bioavailability and is well tolerated, with primarily mild gastrointestinal side effects such as abdominal pain, diarrhea, and nausea. No significant adverse events have been noted in human trials. At present, NTZ has no documented drug-drug interactions as well [53]. Based on the pharmacokinetic parameters of NTZ and the drug's excellent safety profile, Basu and colleagues presented a pilot prospective study at the 2008 American Association for the Study of Liver Diseases (AASLD) meeting showing clinical improvement in HE among cirrhotic patients who

received NTZ and lactulose. Each patient was treated with oral lactulose 30 ml and NTZ 500 mg twice daily for 14 days. Mental status improved 30-70% in 15 patients with an improvement in the QOL score from 20-80%. The regimen was well-tolerated with 3 patients reporting gastric distension and cramps which resolved by taking NTZ with food [29].

The present study is the first prospective, randomized, controlled study to evaluate the efficacy and safety of NTZ compared to metronidazole and rifaximin in patients with grade II-III HE and to evaluate its effect on the improvement of patient's QOL. This study confirms that NTZ is at least as effective as metronidazole and rifaximin in improving HE in Egyptian cirrhotic patients. The duration of the study was 7 days based on other studies that showed clinical improvement in HE patients around this time period [54-56]. There was no need to prolong the duration of study in order to decrease the number of dropout and non-compliant patients.
The current study showed that there was no significant difference between baseline and after 1 week ammonia level among the 3 groups regardless the improvement in their CHESS score. Interestingly, out of the 34 patients 3 (2 with grade II HE and 1 with grade III HE) had even normal baseline serum ammonia level.

These findings is in agreement with Shawcross et al that showed the poor correlation between arterial plasma ammonia levels and the manifestation of HE in patients with cirrhosis [37]. Moreover, the correlation between ammonia concentration and astrocyte swelling is not clear cut and may be modulated by the presence of both hyponatremia [57, 58], and the ability of the brain to buffer ammonia-induced increases in glutamine within the astrocytes by losing osmolytes such as myo-inositol [59]. Moreover, a study by dam et al. did not support a direct toxic effect of hyperammonemia on brain oxidative metabolism but still did not preclude other or indirect roles of ammonia in HE [60].

On the other hand, some studies concluded that raised plasma ammonia level appears to be an important laboratory abnormality seen in HE patients, and it seems to correlate with the severity of encephalopathy [61, 62].

Discrepancies in the direct correlation between ammonia concentration and the severity of HE shows that hyperammonemia may not be solely responsible for the neurocognitive sequelae and other pathophysiological pathways might be contributing [63].

The 3 groups showed significant decrease in CHESS score after 1 week that was reflected clinically by improvement in patient's alertness, orientation and ability to respond and to talk. Similarly, NTZ had the same results in the study conducted by Basu et al. where the patients' performance on Modified Encephalopathy Scale (MES) improved 30-70% in 15 out of 19 patients (79%). This scale comprised mental status, sleep, irritability, confusion, lethargy, tremor, and comprehension [29].

The adverse events reported for the 3 drugs may be explained by the course of the liver disease. Also lactulose treatment may contribute to the GI side effects presented by the patients as shown by several studies. Lactulose had more prominent GI side effects when compared to other treatments [46, 55, 64], and its use as a treatment of HE in everyday clinical practice (that is, outside the controlled conditions of a clinical trial) may be implicated in increased gastrointestinal symptom severity and, consequently, reduced QOL [65].

Nitazoxanide was proved to be well-tolerated in the study by Basu et al., where only 3 out of 19 patients reported gastric distension and cramps which resolved by taking NTZ with food [29]. Other studies reported that NTZ had mild and transient adverse events [18, 66-68]. Moreover, the 4 deaths cases were believed to be a result from the progression of the disease course in these patients.

Regarding the patients' QOL, NTZ significantly improved CLDQ total and fatigue score after 1 week of treatment while other domains did not significantly change. The other two groups did not show significant changes in all CLDQ domains. This was confirmed in the study made by Basu and

colleagues where NTZ also improved the QOL score from 20-80% [29].

CONCLUSION: Administration of 500 mg of NTZ twice daily over 7 days showed the same efficacy on HE as standard treatment. Although, it did not result in significant decrease in serum ammonia level, however, it significantly decreased CHESS score and improved mental status. Moreover, NTZ was superior to standard treatment in improving CLDQ total and fatigue score.

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