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Efficacy and safety of Sodium benzoate as an adjunctive therapy in the management of acute hepatic encephalopathy

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Abstract— Background: Hepatic encephalopathy HE is a neuropsychological disorder in patient with advanced liver disease. The ammonia has a critical role in HE pathogenesis.
The aim: to evaluate efficacy and safety of sodium benzoate (SB) as a cheap adjunctive agent that can be used in addition to rifaximinor lactulose for the treatment of HE. **Methods**: This study included 90 patients of overt HE in 3 groups: Group A (30 patients received oral sodium benzoate capsule and lactulose), group B (30 patients received oral sodium benzoate capsules and rifaximin, and group C (30 patients (control group) received lactulose and rifaximin). Each group was subjected to clinical examination, and laboratory investigations. The three groups evaluated before and after treatment for clinical response using West Haven Criteria classification of HE, Clinical Hepatic Encephalopathy Staging Scale (CHESS) score and psychometric tests. **Results**: There was statistically significant difference in WHC grades of HE, CHESS score of HE, and psychometric tests before and after treatment in each group ($P < 0.05$). There was no statistically significant difference in the overall improvement between the three studied groups after the treatment regarding WHC grades, CHESS score and psychometric tests. No reported significant adverse events.**Conclusion**: Adding SB to either lactulose or rifaximin in the treatment of HE is clinically equivalent to lactulose and rifaximin combination. This finding highlights the therapeutic value of SB as a cheaper medication in treatment of HE.

Keywords: Hepatic encephalopathy (HE), Sodium benzoate (SB),rifaximin,lactulose,West Haven Criteria(WHC), Clinical Hepatic Encephalopathy Staging Scale (CHESS).

Introduction

Hepatic encephalopathy is a neuropsychological disorder in patient with advanced liver disease[1]. The clinical manifestations are greatly changeable, which can reveal mild cognitive or motor weakness firstly, or gradually develop to coma, and in some times death, without treatment[2]. The case is assorted as overt if it is clinically obvious or minimal if only manifest

through psychometric testing[3].The precise pathogenesis of this syndrome is unknown. However, there is an agreement that ammonia has a critical role HE pathogenesis. Ammonia is a neurotoxin that induces a broad range of functional disorder in the central nervous system[4]. Overt HE management includes identifying and handling precipitating factors and decreasing bacterial-derived toxin contents. Lactulose is first-line treatment for acute overt HE. To avoid HE recurrence, lactulose in addition to rifaximin is suggested[5]. However, new medications are under trial[6]. Drugs which aim serum and tissue ammonia metabolism and elimination may be substantial adjuncts to drugs that decrease ammonia output and absorption from the GIT for patients with serious or constant overt symptoms of HE[7]. Sodium benzoate is a cheap adjunctive agent that can be utilized in addition to rifaximin and lactulose and may present a choice for some refractory HE patients who have not responded to usual therapies or who cannot pay for them[7]. The aim of this study was to evaluate the efficacy and safety of SB in treatment of hepatic encephalopathy as an alternative to rifaximin or lactulose.

Subjects and methods

This prospective, randomized controlled study involved 112 consecutive patients with cirrhosis and overt HE who were admitted at the tropical medicine department, Minia University Hospital, Minia, Egypt, in the period from March 2017 to June 2018. Seven patients were not included in the study as they didn't accomplish the inclusion criteria, ten patients were excluded from the study due to lost follow-up, and five patients had not completed the treatment period. 90 Patients were divided randomly into three groups :

Group A: 30 patients were 17 males and 13 females at age group from 32-60y received the following treatment for five days:(Oral sodium benzoate capsules as 3g twice daily, Lactulose 30-60 ml per day, enema, zinc, and branched chain amino acids)

Group B: 30 patients were 16 male and 14 females at age group from 31-65y received the following treatment for five days:(Oral sodium benzoate capsules as 3 g twice daily, rifaximin 550 mg twice daily, enema, zinc,and branched chain amino acids)

Group C: 30 patients were 18 males and 12 females at age group from 35-62y received the following treatment for five days:(Lactulose 30-60 ml per day, rifaximin 550 mg twice daily, enema, zinc,and branched chain amino acids)

Each patient in the three studied groups was subjected for: thorough history taking, clinical examination and laboratory investigations in the form of: CBC, complete liver function, renal function and serum electrolytes. The three groups evaluated before and after treatment for clinical response using West Haven Criteria classification of hepatic encephalopathy[8], Clinical Hepatic Encephalopathy Staging Scale (CHESS) system which classifies the severity of the hepatic encephalopathy on a linear scale that vary from 0 (normal mental state) to 9 (deep coma) according to the answers of the nine questions with the final score is the sum of

the answers to the 9 objects[9] and psychometric tests in the form of (Trail making test part A and Line tracing test).

The collected data were inserted, tabulated, and statistically anatomized using Statistical Package for Social Sciences program (SPSS) software version 24.Qualitative data were expressed as proportions, while quantitative data were expressed as mean + standard deviation (SD). Qualitative data were analyzed by Chi square ($\chi 2$) test. Comparisons between groups for normally distributed quantitative data were performed by Mann-Whitney Test between the two groups. Statistical significance was defined as p values less than 0.05.

Results

Demographic and laboratory data for the studied groups are shown in table (1). There was statistically non-significant difference between the three groups regard demographic and laboratory data. Comparison between WHC grades of HE, CHESS score of HE,and psychometric tests in the three studied groups before and after treatment had completed are shown in table (2), there was statistically significant difference in WHC grades of HE, CHESS score of HE,and psychometric tests before and after treatment in each group ($P < 0.05$). Comparison between group A and control group, and comparison between group B and control group regarding WHC grades, CHESS score and psychometric tests after treatment are shown in table (3), there was no statistically significant difference in grades of WHC, CHESS score, and psychometric tests after treatment between group A and control ($P = 0.1$, $P= 0.13$, $P=0.08$), also, there was no statistically significant difference in grades of WHC, CHESS score, and psychometric tests after treatment between group B and control ($P = 0.05$, $P= 0.1$, $P=0.05$). The overall improvement of all patients after the treatment regarding WHC grades, CHESS score and psychometric tests are shown in table (4), there was no statistically significant difference in overall improvement between the three studied groups. Comparison between serum sodium level in group A and group B before and after treatment are shown in table (5), there was no significant difference in sodium level before and after treatmentin both groups. There were no recorded adverse events .

Discussion

The current study designed to investigate the role of SB in management of acute episodes of overt HE. This novel comparison in our study was designed to assess if SB can replace the other two drugs in combination regimens for treatment of HE keeping in mind the low cost and mild adverse effects of SB when compared with the other two drugs. In the present study, patients treated using SB and lactulose in addition to the standard treatment showed significant clinical improvement in terms of improved HE grade, reduced CHESS score and improved psychometric test. In addition, patients treated with SB and rifaximin combination also achieved significant clinical and psychometric improvement. Similar results were

obtained from patients (control) who were treated with lactulose and rifaximin. In harmony with our data, the study of (Sushma et al., 1992) [10] on 74 consecutive patients with HE. In their prospective randomized double-blind study, 38 patients received sodium benzoate and 36 took lactulose. Thirty patients (80%) receiving sodium benzoate and 29 (81%) receiving lactulose improved; the residual patients died. Enhancement in PSE parameters occurred in both treatment groups and was similar. EEG and evoked potentials were not as useful as mental condition in assessing of improvement. Psychometric test scores stayed abnormal after improvement of mental condition (21 to 42 days) and were possibly too sensible for monitoring of these patients. The prevalence of side effects was comparable in the two treatment groups. The charge of lactulose for one course of treatment was 30 times that of sodium benzoate. Similar results were reported by the study of (Campollo et al 1994) [11]. On the other hand, the study of (Efrati et al, 2000) [12] found different conclusions. In their work, they aimed to assess the ammonia-lowering effect of benzoate in cirrhotic patients without overt hepatic encephalopathy. They noted that after benzoate treatment, the peak increments and basal values of ammonia were notably superior to before. The Number Connection tests were not distorted by benzoate treatment. But the point of weakness in this study is that the investigators did not focus on clinical evaluation of patients. Moreover, they did not include patients with overt HE. In our study, SB administration wasn't associated with significant increase in serum sodium level. This result is supported by the study of (Husson et al., 2016) [13]who used SB for management of urea cycle enzyme disorders for ten years without affecting sodium levels .

Thus, in summary, adding SB to either lactulose or rifaximin in the treatment of HE is clinically equivalent to lactulose and rifaximin combination. This finding highlights the therapeutic value of SB in treatment of HE. It is worth to say that patients with HE who are not tolerating lactulose for flatulence and bloating will get benefit from SB. We think that the marked cheaper price of SB may add socio-economic benefit when replacing rifaximin or lactulose.

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Table(1):The demographic data and laboratory data of the three studied groups

	Group A N=30	**Group B N=30**	**Group C N=30**
Age : **Range (years)** **M ± SD**	(32-60) y 49.33±6.6	(31-65) y 50.07±6.1	(35-63) y 51.7±5.3
Gender: **Male:** **Female:**	17 (56.67%) 13 (43.33%)	16 (53.33%) 14 (46.67%)	18 (60%) 12 (40%)
Smoking: **No.** **Yes.** **Ex smoker.**	15 (50%) 9 (30%) 6 (20%)	17 (56.67%) 7 (23.33%) 6 (20%)	13 (43.33%) 10 (33.33%) 7 (23.33%)
Residence: **rural** **urban**	26 (86.67%) 4 (13.33%)	24 (80%) 6 (20%)	23 (76.67%) 7 (23.33%)
Educational level: **Good** **Fair**	7 (23.33%) 23 (76.67%)	10 (33.33%) 20 (66.67%)	8 (26.67%) 22 (73.33%)
Bilirubin (mg/dl): **M ± SD**	1.861±0.3827	1.29±0.498	2.220±0.4612
Albumin (g/dl): **M ± SD**	2.973±0.2196	2.923±0.2861	2.517±0.2167
Creatinine (mg/dl): **M ± SD**	1.190±0.1647	1.160±0.1429	1.210±0.1668
Urea (mg/dl): **M ± SD**	38.033± 6.0200	37.667±6.5408	37.733±5.9186
K level (mmol/l): **M ± SD**	4.523±0.5070	4.413±0.4659	4.633±0.3916
Na level (mmol/l): **M ± SD**	128.7±4.4	128.5±4.5	130.100±4.3419
INR : **M ± SD**	1.190±0.2040	1.283±0.2245	1.610±0.1583

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Table (2): Comparison between before and after treatment of each group A, B, C regarding WHC grades, CHESS score and psychometric tests.

	A			B			C		
	Before treatment	**After treatment**	**P value**	**Before treatment**	**After treatment**	**P value**	**Before treatment**	**After treatment**	**P value**
WHC grades	3.4	1.9	0.04	3.5	1.8	0.037	3.6	2	0.025
CHESS score	7.1	1.9	0.02	7.3	1.5	0.024	7.4	2	0.031
Psychometric tests	2	1.1	0.031	2	1.2	0.018	2	1.3	0.025

Table (3): Comparison between group A and group C and comparison between group B and group C regarding WHC grades, CHESS score and psychometric tests.

	Group A	**Group C**	**P value**	**Group B**	**Group C**	**P value**
WHC grades	27.15	33.85	0.1	26.67	34.33	0.059
CHESS score	27.48	33.49	0.138	27.62	33.38	0.15
Psychometric tests	27.5	33.5	0.082	27	33.9	0.054

Table (4): The overall improvement of all patients after the treatment regarding WHC grades, CHESS score and psychometric tests

	After Treatment	**Mean Rank**	**P value**
Overall Improvement	**Group A**	40.07	**0.059**
	Group B	38.32	
	Group C	39.5	

Table (5): serum sodium level in group A and group B before and after treatment

	Na on admission (mmol/l)	Na on recovery (mmol/l)	P value
Group A : **Range** **M ± SD**	(119-137) 128.9±4.4	(120-135) 128.7±4.4	0.056
Group B : **Range** **M ± SD**	(121-136) 128.6±5.1	(123-135) 128.5±4.5	0.62

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