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Congress report

Rifaximin versus metronidazole in management of acute episode of hepatic encephalopathy: An open labeled randomized clinical trial

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ABSTRACT

Background and study aims: Many regimens are tried in managing overt hepatic encephalopathy (HE). We investigated the efficacy of rifaximin versus metronidazole in management of an acute episode of HE on top of cirrhosis.

Patients and methods: An open label prospective controlled trial was conducted on patients with an acute episode of HE on top of cirrhosis who were randomly divided into metronidazole-group (M-group) and rifaximin-group (R-group) with 60 patients in each.

The main outcome measure was the clinical improvement of HE, duration of hospital stay and the changes in the level of serum ammonia after 3 days of starting therapy.

Results: Both M-group and R-group were comparable as regards age and sex (mean age 51 ± 11 years and 49 ± 12; male/female ratio 45:15 and 50:10, respectively). Forty-six patients (76.7%) in M-group compared with forty-five (75%) in R-group showed clinical improvement (p = 0.412). Hospital stays were comparable between both group; 4.2 ± 2.1 and 3.9 ± 1.7 for M-group and R-group; respectively (p = 0.435). There was no significant difference of venous ammonia levels (Mean of delta 160.77 ± 185.34 μg/dL and 207.95 ± 218.43 μg/dL with p 0.664 and 0.974 in M-group and R-group, respectively). No adverse events were reported throughout the whole study.

Conclusion: Rifaximin and metronidazole are equally effective in management of acute episode of overt HE, therefore, re-auditing of treatment protocols of HE are warranted especially in limited resource settings.

Introduction

Hepatic encephalopathy (HE) remains one of the major indications of frequent admissions and a lethal fate in most of patients with end-stage liver disease [1,2]. This burden is more profound especially in areas with a high prevalence of post-hepatitic cirrhosis like in Egypt [3,4].

Till now, there is no single hypothesis or theory which can govern the pathogenetic mechanism of HE. Of these mechanisms, the toxic effect of ammonia derived from the gut-flora on the mental state represents the main acceptable theory [5]. Therefore, studying different regimens of gut-cleaning agents and the different antimicrobial drugs were thoroughly investigated aiming to decrease the growth of ammonia-producing flora, and hence, decrease the ammonia production and subsequent mental changes [6].

Metronidazole, is considered as the earlier drug used to treat acute episodes of overt HE [7]. Also, the relatively new drug; rifaximin was extensively studied in this context [8]. The cost effectiveness of the different regimens is a matter of discussion, even in developed countries [9,10].

So, we herein, tried to evaluate the efficacy of a short-term regimen of rifaximin versus metronidazole in acute episodes of overt hepatic encephalopathy and their effect on ammonia level before and after treatment.

Patients and methods

Patients' recruitment

Between January 2017 and August 2017, a prospective open labeled randomized clinical controlled trial was conducted to enroll cirrhotic patients admitted to Assiut University Hospital, Department of Gastroenterology and Hepatology with an acute episode of overt hepatic encephalopathy on top of cirrhosis.

Abbreviations: AASLD, the American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; HE, hepatic encephalopathy; LOLA, L-ornithine L-aspartate; WHC, West Haven criteria.

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Exclusion criteria were age less than 18 years, known major psychiatric illness, intestinal obstruction, serum creatinine level >1.5 mg/dl, prior porto-systemic shunt placement, hepatocellular carcinoma, and/or has hypersensitive to any drug used in the study. Also, patients who received any anti-encephalopathy measure prior to admission and those died before the 3rd day of enrollment were excluded.

Study design

Patients were subjected to thorough history taking (from the patients' relatives or patients themselves if possible), clinical examination and basic laboratory tests to evaluate co-morbidities, to detect precipitating factors (e.g. infections, diarrhoea, vomiting, diuretics intake, constipation, high protein diet, gastrointestinal bleeding and large volume paracentesis), and to calculate Child Pugh Turcotte (CPT) and Model for End-Stage Liver Disease (MELD) scores.

Eligible patients were subjected to a 1:1 randomization into two groups; the M-group and the R-group.

The *M-group* consists of patients treated with oral metronidazole (250 mg) three times/day. The *R-group* consists of patients treated with oral rifaximin (400 mg) three times/day. Both groups received a concomitant fixed basic regimen of oral lactulose (15–30 ml) 2–3 times/day till the passage of 2–3 loose stools daily, L-ornithine -L-aspartate (LOLA; either 10 mg intravenously twice daily or 9–18 mg orally divided on 3 equal doses daily), and magnesium sulfate enema 3 times daily if there is no contraindication.

The severity of HE was graded according West Haven Criteria (WHC) [11] at time of presentation and before starting treatment by a single dedicated hepatologist (A.R.R.) who performed this test through out the study.

Changes in the serum ammonia levels were assessed at the time of admission and 3 days after therapy in all patients (reference range 19–60 μg/dL (11–35 μmol/L; according to the manufacture supply (BIOLABO®, kit REF No 99261, France).

Study end points

The primary end point of study was the change in the grade of HE after 3 days of admission using WHC (the reversal of HE). The secondary end point was the length of hospital stay.

Potential adverse events of both regimens were observed throughout the study.

Data analysis and ethical considerations

The clinical and laboratory data were categorized and processed using the Statistical Package for Social Sciences, version 19 (SPSS Inc., Chicago, Illinois, USA). All of our data were non-parametric. Wilcoxon rank test and Mann–Whitney *U* test were used to compare means. Categorical data were analyzed by the *Chi-square* test and Fisher's exact test. A *p* value less than 0.05 was considered statistically significant.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by institutional ethical committee. An informed written consent was taken from the patients' relatives.

Result

Patients' characteristics (Table 1)

A total of 120 patients (95 patients were males (79.17%) and the mean age was 50 ± 11.3 years) were enrolled. There was no statistically significant difference between M-group and R-group in terms of age, sex, associated co-morbidities, grades of HE and precipitating factors. Most of patients presented with HE grade I and II. Infections, diarrhoea and excessive use of diuretics were the chief precipitating factors.

No statistically significant difference was found between groups in the CPT score (10.7 ± 3.5 and 11.2 ± 1.6 for M and R-group, respectively) and in MELD score (20.5 ± 6.3 and 21.8 ± 5.5 in M and R-group, respectively). Most of the patients were category C (47 patients and 51 patients in M and R-group, respectively).

Primary end-point (Fig. 1, Table 2)

The overall clinical improvement after 3 days of admission by WHC assessment was in 91 patients (75.8%) while 29 of the patients (24.2%) showed no clinical improvement. There is no statistical difference in improvement rate between M and R-group; 75% and 76.7% in M-group and R-group, respectively (p = 0.5).

Ammonia level changes (Fig. 2, Table 3)

Pre-treatment, all patients had elevated serum ammonia levels with a comparable non significant mean value (p = 0.453). Also, there was no correlation between grade of encephalopathy and serum ammonia level (r = 0).

Table 1
Demographic and clinical data of the study groups.

Variables	Group M (n = 60)	Group R (n = 60)	p-value±
Mean of age (years)	51 ± 11	49 ± 12	0.981 (NS)
Sex M:F	45 (75%): 15 (25%)	50 (83.33%):10 (16.67%)	0.765 (NS)
Co-morbidities			
None	40 (66.67%)	45 (75%)	0.213 (NS)
DM	8 (13.34%)	10 (16.67%)	
Hypertension	5 (8.33%)	4 (6.67%)	
IHD	4 (6.67%)	1 (1.66%)	
CKD	3 (4.99%)	0	
Grades of HE*			
I	32 (53.33%)	28 (46.66%)	0.423 (NS)
II	13 (21.67%)	22 (36.67%)	
III	6 (10%)	7 (11.67%)	
IV	9 (15%)	3 (5%)	
Precipitating factors			
Infections	22 (36.67%)	24 (40%)	0.276 (NS)
Diarrhoea	14 (23.33%)	9 (15%)	
Diuretics	10 (16.67%)	7 (11.66%)	
Constipation	5 (8.33%)	6 (10%)	
High protein diet	4 (6.67%)	6 (10%)	
Vomiting	2 (3.33%)	4 (6.67%)	
LVP	2 (3.33%)	3 (5%)	
No factor	1 (1.67%)	1 (1.67%)	
CPT Score			0.423 (NS)
A	0	0	
B	13 (21.67%)	9 (15%)	
C	47 (78.33%)	51 (85%)	
MELD score	20.5 ± 6.3*	21.8 ± 5.5*	0.210 (NS)

Abbreviations: HE; hepatic encephalopathy, MELD; Model for End-Stage Liver Disease, CPT; Child-Pugh Turcotte, NS; not significant, DM; Diabetes mellitus, IHD; Ischemic heart disease, CKD; Chronic kidney disease, LVP; Large Volume Paracentesis.

* Using West Haven Criteria (WHC).

± Mann–Whitney *U* test for age and MELD score, Chi square and Fisher's exact test for other parameters.

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