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# Effect of Helicobacter Pylori Eradication on Hepatic Encephalopathy in Egyptian Cirrhotic Patients

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## Abstract

*Background:* Much ammonia is produced by helicobacter pylori and by its eradication, the grade of hepatic encephalopathy could be improved.

*Aim of Study:* To evaluate the effect of H. pylori eradication on the stage of hepatic encephalopathy.

*Patients and Methods:* This study included 80 cirrhotic patients infected with H. pylori which was diagnosed by stool antigen. The studied patients were further subdivided into groups according to the regimen of H. pylori eradication. Follow-up was done after one month to assess the effect of its eradication on the improvement of hepatic encephalopathy.

*Results:* Follow-up after one month of treatment revealed that the eradication rate for H. pylori showed higher efficacy with Levofloxacin based therapy (89.47%) compared to Clarythromycin regimen (76.47%) with $p$-value=0.3. Most of cirrhotic patients with hepatic encephalopathy improved after successful eradication however without a statistical significance.

*Conclusions:* Our results showed that H pylori eradication may improve the grade of hepatic encephalopathy.

***Key Words:*** *Liver cirrhosis – Hepatic encephalopathy – H. Pylori eradication.*

## Introduction

**HELICOBACTER** pylori (H. pylori) infection is reaching over 70% in developing countries. This infection has been associated with various gastrointestinal diseases [1]. It was reported that H. pylori in Egyptian patients with cirrhosis was higher than those without cirrhosis [2].

Hepatic encephalopathy (HE) is a serious and frequent complication of liver cirrhosis; the pathophysiology of this complication is not completely understood. Among the leading precipitating factors are increased blood ammonia levels [3]. Previous studies showed that after H.pylori eradication, grade of hepatic encephalopathy has improved [4].

The aim of this study was to evaluate the role of H. pylori eradication in the improvement of HE in cirrhotic patients.

## Patients and Methods

The present study included 80 cirrhotic patients based on clinical, laboratory and abdominal ultrasonographic findings. They infected with H pylori which diagnosed by stool antigen (BIONEXIA® H. pylori Ag, 415669, bioMérieux Asean, China). They were selected from hepatology department and outpatient clinic of Ahmed Maher Hospital, Cairo, Egypt. Over a period of one year from 2017 to 2018.

They were above 18 years old, they had hepatic encephalopathy grade I or II. The diagnosis of hepatic encephalopathy was based on clinical findings mostly in the form of tremors and slurred speech. The exclusion criteria were; the presence of active bleeding, active infection, hepatocellular carcinoma (HCC), renal impairment (Cr >2mg/dl), recent PPI and antacids, and other causes of encephalopathy such as: Encephalitis, hyperglycemia or hypoglycemia and acute fulminant hepatic failure, electrolyte imbalance. A written consent was obtained before enrollment in the study.

The encephalopathic patients were subdivided into 20 patients ( HEA1) who received treatment to H. pylori (PPI in its standard dose combined with amoxicillin 1gm bid and clarithromycin 500 mg bid) for 10 days [5], and 20 patients (HEA2) received another treatment regimen to H. pylori

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(standard dose of PPI, Amoxicillin 1gm bid and Levofloxacin 500mg once a day) for 10 days [6], while the remaining 40 patients (HEB) did not receive treatment for H. pylori.

For follow-up after eradication we also used H pylori stool antigen kit (BIONEXIA® H. pylori Ag, 415669, bioMérieux Asean, China), after one month from completing treatment regimen.

*Statistical analysis:*

Numerical data were expressed as mean and standard deviation. For quantitative variables, comparison between two groups was done using *t*-test, and for 3 groups or more ANOVA test was used. Qualitative data were expressed as frequency and percentage. *p*-value is considered to be significant if <0.05 and highly significant if <0.001.

## Results

Among the studied patients, age ranged from 38 to 68 years, the mean age was 54.6 ±7.58 SD with female predominance (52%). Table (1).

Table (1): Demographic characteristics of the studied groups.

| Gender | HEA1 | | HEA2 | | HEB | | *p* value |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | |
| Male | 10 | 50.0 | 10 | 50.0 | 18 | 45.00 | 0.87 |
| Female | 10 | 50.0 | 10 | 50.0 | 22 | 55.0 | |
| Total | 20 | 100 | 20 | 100 | 40 | 100 | |
| Age | | | | | | | |
| Range | 45-68 | | 43-66 | | 38-67 | | |
| Mean ± SD | 55.9±6.16 | | 56.35±7.29 | | 56.6±7.93 | | |

Table (2) shows the Child score of the studied groups.

Table (2): Child score of the studied cirrhotic groups.

| | Child score | | Anova | |
|---|---|---|---|---|
| | Range | Mean ± SD | F | *p* |
| HEA1 | 11-14 | 12.75±0.91 | 24.99 | 0.07 |
| HEA2 | 11-14 | 12.70±1.17 | | |
| HEB | 10-14 | 12.30±0.97 | | |

After one month of treatment, three patients from group HEA1, and one patient from group HEA2 were lost their follow-up. The eradication rate for H. pylori by per protocol (PP) analysis for HEA1 group was (76.47%) compared to (89.47%) for group HEA2. There was no significant difference between the two groups however the line of treatment with levofloxacin had higher efficacy. Table (3) & Fig. (1).

Table (3): The efficacy of treatment regimens.

| Stool antigen | Group | | | | | | *p*-value |
|---|---|---|---|---|---|---|---|
| | HEA1 | | HEA2 | | Total | | |
| | N | % | N | % | N | % | |
| Negative (Eradicated) | 13 | 76.47 | 17 | 89.47 | 30 | 83.33 | 0.296 |
| Positive (not eradicated) | 4 | 23.53 | 2 | 10.53 | 6 | 16.67 | |
| Total | 17 | 100.00 | 19 | 100.0 | 36 | 100.00 | |

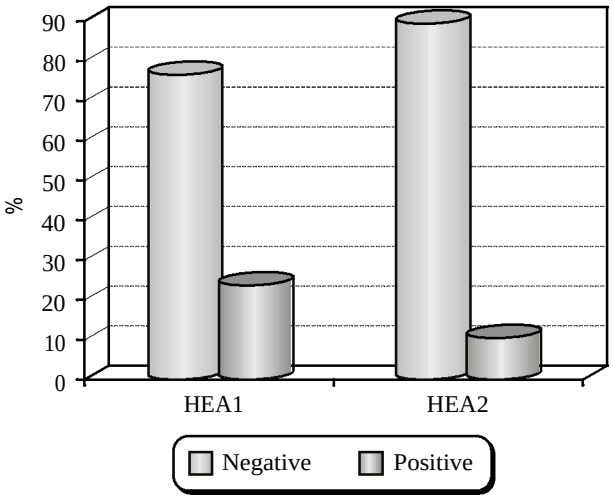


Fig. (1): The efficacy of treatment regimens.

Follow-up data of the studied patients in relation to treatment response showed that the grading of encephalopathy before treatment among HEA1 was 80% grade I and 20% grade II. After eradication; 13 patients were eradicated (8 patients 61.54% recovered, 4 patients 30.77% were grade I and one patient 7.69% was grade II) while 4 patients were not eradicated and 3 patients were missed their follow-up (3/7 recovered; 42.8% and 1/7 was grade II; 14.4%).

Regarding HEA2 we found 75% were grade I and 25% were grade II. After eradication; 17 patients were eradicated (1 1 patients 64.71% recovered, 3 patients 17.65% were grade I and 3 patients 17.65% were grade II),while 2 patients were not eradicated and one patient missed the follow-up (one patient recovered 1/3; 33.3% and 1/3 was grade 1; 33.3%).

As regards HE B of them 65% were grade I and 35% were grade II. On follow-up without eradication of H. pylori 21 patients recovered (52.5%), Eleven patients were grade I (27.5%) and 2 patients were grade II (5%) and 6 patients missed the follow-up. Table (4) & Fig. (2).

Table (4): Follow-up data of the studied patients in relation to treatment response.

| | Group | | | | | | | | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| | HEA1 | | HEA2 | | HEB | | Total | | |
| | N | % | N | % | N | % | N | % | |
| *Grading of HE:* | | | | | | | | | |
| Grade I | 16 | 80.00 | 15 | 75.00 | 26 | 65.00 | 57 | 71.25 | 0.43 |
| Grade II | 4 | 20.00 | 5 | 25.00 | 14 | 35.00 | 23 | 28.75 | |
| Follow-up grading *Eradicated:* | | | | | | | | | |
| Recovered | 8 | 61.54 | 11 | 64.71 | 0 | 0.00 | 19 | 63.3 | 0.57 |
| Grade I | 4 | 30.77 | 3 | 17.65 | 0 | 0.00 | 7 | 23.3 | |
| Grade II | 1 | 7.69 | 3 | 17.65 | 0 | 0.00 | 4 | 13.3 | |
| *Not eradicated:* | | | | | | | | | |
| Not follow-up | 3 | 42.8 | 1 | 33.3 | 6 | 15.00 | 6 | 13.04 | 0.52 |
| Recovered | 3 | 42.8 | 1 | 33.3 | 21 | 52.50 | 25 | 54.35 | |
| Grade I | 0 | 0.00 | 1 | 33.3 | 11 | 27.50 | 12 | 26.09 | |
| Grade II | 1 | 14.4 | 0 | 0.00 | 2 | 5.00 | 3 | 6.52 | |

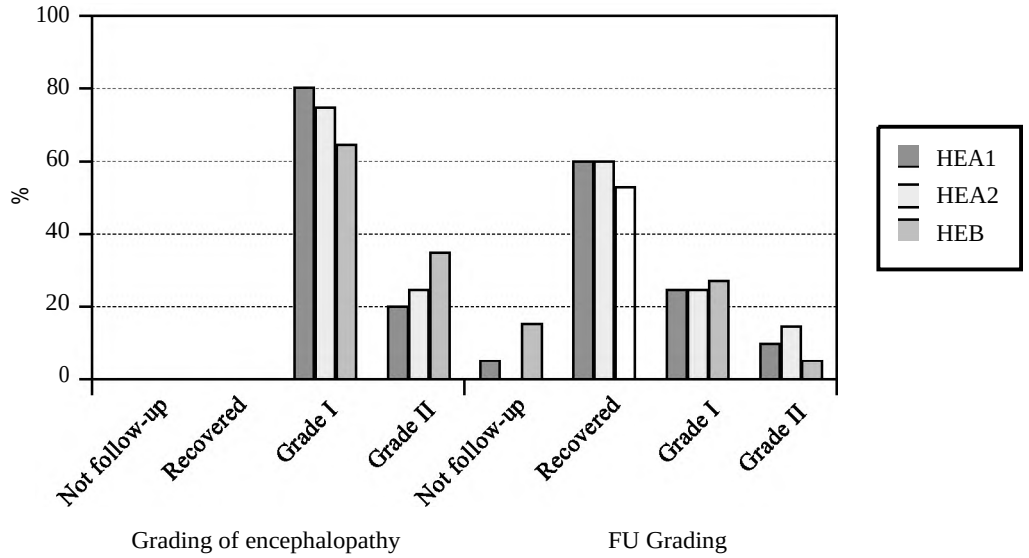


Fig. (2): Follow-up data of the studied patients in relation to treatment response.

## Discussion

Previous studies on the association of H. pylori infection with HE and on the reduction of ammonia by H. pylori eradication have not been conclusive [7].

In the current study we aimed to investigate the impact of H. pylori eradication on the severity of hepatic encephalopathy.

Previous studies found that patients with H. pylori infection had significantly higher gastric juice ammonia concentrations than those without infection, however they stated that H. Pylori infection does not seem to play a major role in the pathogenesis of hyperammonemia in cirrhotic patients [8,9]. There may be a relationship between H Pylori and HE in cirrhosis. Eradicating H Pylori may be beneficial for the clinical prevention and treatment of HE in liver cirrhosis [10]. On the other hand, a study was done by Miquel et alwho found that the diffuse distribution of H pylori in the stomach contributes partly to hyper ammonia in patients with liver cirrhosis [11]. Others stated that ammonia production in stomach which does not increase blood level of ammonia in normal persons, can elevate the ammonia level in blood of cirrhotic patients because of reduction in ammonia metabolism [12].

In addition to Abdel Hady et al., who documented a significant increase in plasma endotoxin in

association with H.pylori infection in cirrhotic patients **[13]**. Which is cytotoxic on the endothelial cells of the blood-brain barrier in vitro.

Theoretically these differences may be due to the effect of child score or microbe density that generally has not been evaluated. In one study on cirrhotic patients by Zullo et al., inhibitory effect of urease activity on decrease of blood ammonia was seen only in patients with child-Pugh B/C and high density microbe **[14]**.

The choice of the optimal regimen for H. pylori eradication is debated. The standard triple therapy (STT) using amoxicillin, clarithromycin and omeprazole, is one of the widely used regimens for H. pylori eradication. Levofloxacin based therapy (LBT) were used as rescue regimens in case of failure with standard regimen **[15]**.

The results of the present study showed a higher eradication of H. pylori in patients who received Levofloxacin based therapy HE A2 (89.47%) when compared to those administered Standard triple therapy HEA1 (76.47%), but statistical analysis failed to show any significance in these differences ($p$-value=0.3). These results were in agreement with other studies **[16,17]**.

In our study we performed grading of encephalopathy after one month of treatment of H pylori and we found improvement of HE grade as among HEA1 we had 13 patients with H. pylori eradication of them 8 patients (61.54%) recovered, also in HEA2 we found 11 patients out of 17 recovered (64.71%) however did not show significant relation to eradication of H pylori and that was in agreement with other studies **[18,19]**. In addition to the 40 cirrhotic patients who did not receive eradication 21 of them recovered (52.5%). Moreover the not eradicated patients showed recovery as in HEA1 and HEA2 (3/7; 42.8% & 1/3; 33.3%) respectively.

Similarly a study done by Agrawal et al., has concluded that there was improvement in psychometric tests and improved manifestations of MHE after H pylori eradication. The absence of significant relation between eradication and HE grading may be due to the effect of child score as most of our patients were child C in comparison to child score of the other study which were A and B **[19]**.

Concerning the 40 cirrhotic patients who did not receive treatment for H. pylori, they received the proper line of treatment after one month follow-up.

*Conclusions:*

Our results showed that H pylori eradication may improve the grading of hepatic encephalopathy.

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# تأثير ابادة هيليكوباكتر بيلورى على اعتلال الدماغ الكبدى فى مرضى التليف الكبدى المصريين

خلفية البحث: يتم إنتاج من الأمونيا عن طريق هيليكوباكتر بيلورى H. pylori، ومن خلال القضاء عليها، يمكن تحسين درجة الاعتلال الدماغى الكبدى.

الهدف من البحث: لتقييم تأثير القضاء على هيليكوباكتر بيلورى H. pylori على مرحلة الاعتلال الدماغى الكبدى.

المرضى وطرق البحث: هذه الدراسة شملت ٨٠ مريض تليف الكبد مصابين بالبكتيريا الحلزونية البوابية H. pylori والتى تم تشخيصها عن طريق البراز AG. تم تقسيم المرضى الخاضعين للدراسة إلى مجموعات أخرى وفقاً لنظام القضاء على هيليكوباكتر بيلورى H. pylori تمت المتابعة بعد شهر واحد لتقييم أثر ابادتها على مرحلة اعتلال الدماغ الكبدى.

النتائج: المتابعة بعد شهر واحد من العلاج، أظهرت معدل علاج هيليكوباكتر بيلورى H. pylori فعالية أعلى مع العلاج القائم على الليفوفلوكساسين (٨٩.٤٧٪) مقارنة بنظام الكلاريثروميسين (٧٦.٤٧٪) مع قيمة $p$=0.3 تحسن معظم مرضى التليف الكبدى المصابين بالاعتلال الدماغى الكبدى بعد العلاج الناجح ولكن بدون دلالة إحصائية.