10.5005/jp-journals-10018-1053
ORIGINAL ARTICLE

Correlation between Blood Ammonia Level and Esophageal Varices in Patients with Cirrhosis of Liver

Mohammad Faiz Ahmad Khondaker, Nooruddin Ahmad, Mamun Al-Mahtab, Sharmin A Sumi

ABSTRACT

Portal hypertension leads to the formation of portosystemic collateral veins in cirrhosis of liver. Rupture of esophageal varices is common and can be fatal. Although ammonia plays a certain role in determining portosystemic encephalopathy, the venous ammonia level has not been found to correlate with the presence or severity of this entity. So, this concept has become partially obsolete. Realizing the need for noninvasive markers mirroring the presence of esophageal varices in order to reduce the number of endoscopy screening, this study is aimed to determine whether there is a correlation between blood ammonia concentrations and the size of esophageal varices.

This was a cross-sectional study conducted upon 40 consecutive cirrhosis patients and 40 age-matched noncirrhotic control subjects. Fasting blood ammonia was measured in both groups and upper gastrointestinal endoscopy was done in cirrhotic patients to note different sizes of esophageal varices. Cirrhosis patients group had mean ammonia level of 84.88 μmol/l compared to 28.47 μmol/l in control group ($p < 0.05$). The mean (± SD) blood ammonia concentration in small esophageal varices group was 72.00 (± 39.13) μmol/l and that in medium or large esophageal varices group was 97.75 (± 31.34) μmol/l. The difference was significant at p-value <0.05 level. Among blood ammonia, platelet count and spleen longitudinal diameter (SLD) on ultrasonography (USG), only ammonia level positively correlated with size of varices ($p = 0.004$). There was a moderate but significant correlation between blood ammonia level and size of esophageal varices. So, this could be a good tool for identifying individuals with large esophageal varices who will need to undergo endoscopy more frequently.

Keywords: Esophageal varices, Portosystemic collaterals, Ammonia, Upper gastrointestinal endoscopy.

How to cite this article: Khondaker MFA, Ahmad N, Al-Mahtab M, Sumi SA. Correlation between Blood Ammonia Level and Esophageal Varices in Patients with Cirrhosis of Liver. Euroasian J Hepato-Gastroenterol 2013;3(1):10-14.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Portal hypertension is a progressive, inevitable consequence of cirrhosis of liver, which accounts for most of the severe complications of cirrhosis. Portal hypertension leads to the formation of portosystemic collateral veins. Among them, esophageal varices have the greatest clinical impact because their rupture results in variceal hemorrhage that can be fatal. Upper gastrointestinal (GI) endoscopy is the gold standard in the diagnosis of esophageal varices.

Gastroesophageal varices are present in approximately 50% of patients with cirrhosis. Their presence correlates with the severity of liver disease. Patients without varices develop them at a rate of 8% per year[1,2] and the progression from small to large varices occurs in 10 to 20% of cases yearly.[3] Variceal hemorrhage occurs at a yearly rate of 5 to 15%. The most important predictor of hemorrhage is the size of varices, with the highest risk of first hemorrhage (15% per year) occurring in patients with large varices.[4] The risk of first variceal bleeding in patients with large- or medium-sized varices is significantly reduced by beta blockers (30% in controls *vs* 14% in beta blocker–treated patients).[5]

On the basis of these studies recent practice guidelines have recommended that all patients with cirrhosis undergo screening upper GI endoscopy to detect esophageal varices at the time of diagnosis and after that, surveillance endoscopies should be performed every 2 to 3 years in cirrhotic patients without varices and that patients with small varices be endoscoped every 1 to 2 years, and annually in the setting of decompensation.[6,7]

However, these guidelines have not been evaluated prospectively to date, particularly regarding its cost-effectiveness. Since, the point prevalence of medium/large varices is approximately 15 to 25%,[8] the majority of subjects undergoing screening endoscopy either do not have varices or have varices that do not require prophylactic therapy. In other words, a large number of patients will be subjected to unnecessary, invasive procedures. Therefore, the identification of nonendoscopic, noninvasive methods that can accurately predict esophageal varices, particularly medium/large esophageal varices in cirrhotic patients and help identify patients at greatest risk and thereby reduce the necessity of endoscopic screening.

Several studies have evaluated possible noninvasive markers of esophageal varices in patients with cirrhosis, such as the platelet count, fibrotest, spleen size, portal vein diameter and transient elastography.[9,10] The predictive accuracy of noninvasive markers so far studied is still unsatisfactory.[10]

The raised blood ammonia level found in cirrhotic patients has long been thought to be responsible for portosystemic encephalopathy (PSE). However, analysis shows that venous ammonia levels cannot serve as a laboratory marker for PSE, for being neither specific nor highly sensitive,[11] although there may be a correlation with

severity.[12] In cirrhosis, the major portion of ammonia carried by portal blood is shunted by portosystemic collaterals into systemic circulation. This raised blood ammonia level, on the other hand, could be a good mirror of portosystemic collaterals as well as portal hypertension.

A recent study upon 153 consecutive patients with liver cirrhosis of various etiologies have shown that blood ammonia level correlates well with the severity of liver disease as well as with the presence of different portosystemic shunts, particularly esophageal varices of different grades.[13] The sensitivity and specificity of ammonia in predicting esophageal varices presence was 97 and 43% respectively with the cutoff value of ammonia 42 μmol/l.

The present study was intended to see the correlation of blood ammonia level with esophageal varices in patients with cirrhosis of different etiologies in Bangladeshi population. Establishing such correlation would lead cirrhotic patient with high ammonia level to suspicion of having varices, particularly medium or large varices. This will pinpoint patients who will require closer follow-up and endoscopic screening and who will require follow-up and endoscopic screening less frequently.

MATERIALS AND METHODS

This cross-sectional study was carried out in the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University (BSMMU) during the period of July 2009 to June 2010. A total of 80 consecutive patients were included in the study. Study population was grouped as group 1: 40 patients with cirrhosis of liver with evidence of esophageal varices and group 2: 40 patients without liver disease and no endoscopic evidence of esophageal varices, served as control. Group 1 was again divided into two subgroups according to the size of esophageal varices as group 1A: Cirrhotic patients with small esophageal varices and group 1B: Cirrhotic patients with medium and large esophageal varices. Inclusion criteria were; cirrhosis of liver with esophageal varices irrespective of etiology and severity. Diagnosis of cirrhosis was based on, clinical features suggestive of cirrhosis of liver, ultrasonographic evidence of small-sized liver with coarse echotexture, and/or endoscopic evidence of esophageal varices. Exclusion criteria were, patients who received endoscopic variceal ligation (EVL) or sclerotherapy, presence of hepatic encephalopathy, active or recent GI bleeding within 4 weeks, portal vein thrombosis on ultrasonography (USG), hepatocellular carcinoma, renal insufficiency evidenced by serum creatinine of >1.3 mg/dl and patients in whom endoscopy is contraindicated.

Patients seeking treatment in outpatient and inpatient Department of Hepatology, BSMMU were assessed with detailed clinical history and examination. Patients suggestive of cirrhosis and patients with prior diagnosis of cirrhosis were provisionally selected for the study.

Patients were then evaluated. Liver function tests, serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time, serum albumin were checked and renal function was assessed by estimating serum creatinine. Complete blood count including platelet count and relevant investigations to find out the cause of cirrhosis were done in absence of previous documents. USG of whole abdomen were done to see the size and echotexture of liver, splenomegaly with spleen longitudinal diameter (SLD) and to rule out hepatocellular carcinoma, portal vein thrombosis. Then after full explanation about the study, they were asked for participating in the study and informed written consents were taken.

Endoscopy of upper GIT was done by Olympus video endoscope at Endoscopy Center of BSMMU. During endoscopy, evidence of esophageal varices, gastric varices and portal hypertensive gastropathy were noted. If esophageal varices were found, number and size of varices and presence of any red sign were meticulously surveyed. Varices were classified by the widely used semiquantitative morphological assessment into small (F1), medium (F2) and large (F3) varices.

Control subjects (group 2) were selected from patients seeking treatment for nonulcer dyspepsia, peptic ulcer disease, irritable bowel syndrome with normal renal function and having no liver-related diseases and no varices due to noncirrhotic portal hypertension.

Fasting blood ammonia level was measured in both groups 1 and 2 patients within 1 to 3 days of performing endoscopy. Patients were asked to fast overnight. In the morning, at complete rest, 5 ml of peripheral venous blood was taken from each subject without using tourniquet. Blood was collected into an EDTA evacuated tube. The samples were immediately carried to laboratory gently in an icebox and analyzed within 30 minutes of arrival. In cases of ambulant patient, samples were collected in the laboratory. During analysis, sample was first centrifuged and the plasma was separated from cellular material. Ammonia level was quantified in the plasma by the VITROS AMON slide method using VITROS AMON slides and the VITROS chemistry products.

All the patient details and study variables were entered in predesigned data collection sheet.

Data were analyzed by using statistical software SPSS 13.0. All the quantitative data were expressed as mean ± SD, qualitative data were analyzed by Chi-square test or

Fisher's exact test where appropriate and quantitative data by Student's t-test or Mann-Whitney's U test. Correlation study was done by using Spearman's correlation coefficient test. Performance of the test was assessed by sensitivity, specificity. Receiver operating characteristic (ROC) curve was used to assess the usefulness of the test and performance at different cutoff values. A 'p' value of <0.05 was taken as statistically significant.

RESULTS

The mean (±SD) age was 42.83 (±13.49) years in cirrhosis patients and 39.42 (±12.55) years in control subjects (range: 17-70 years in both groups). Male predominance was noted in both the groups being 90 and 63.3% in groups 1 and 2 respectively. Most of the cirrhosis patients (82.5%) of the study were related to HBV infection while only 12.5% were due to HCV infection (anti-HCV positive) and 5.0% due to other causes. The range of blood ammonia level in group 1 (cirrhosis patients) was 13 to 208 µmol/l and in group 2 (control) was 10 to 63 µmol/l. Group 1 had mean ammonia level of 84.88 µmol/l compared to 28.47 µmol/l in group 2 (p = 0.001). The mean (±SD) blood ammonia concentration in group 1A (small esophageal varices) and group 1B (medium or large esophageal varices) was 72.00 (±39.13) µmol/l and 97.75 (±31.34) µmol/l with range from 13 to 107 µmol/l and 48 to 208 µmol/l respectively. The mean difference was significant at p-value < 0.05.

Platelet count and SLD on USG (SLD on USG) did not show significant difference between groups 1A and 1B (p > 0.05). Among blood ammonia, platelet count and SLD on USG, only ammonia level positively correlated with size of varices (p = 0.004) (Table 1). Blood ammonia level 63 µmol/l had sensitivity of 95% and specificity of 50% in detecting medium and/or large esophageal varices in patients with cirrhosis; positive predictive value (PPV) was 65.5 µmol/l and negative predictive value (NPV) was 90.9 µmol/l with accuracy of 72.5% (Table 2). If cutoff value was raised further, sensitivity declined and specificity increased (Fig. 1). In relation to detection of large size varices by means of a noninvasive marker, sensitivity is more important than specificity. So cutoff value 63 µmol/l was found better than other values.

DISCUSSION

The present study was conducted to assess usefulness of blood ammonia level as a noninvasive marker for predicting size of esophageal varices particularly the large size varices in patients with cirrhosis.

Blood ammonia values were estimated in cirrhotic group and control group. The study showed there was significant difference between the mean ammonia level of cirrhotic and control group (p = 0.001). The mean ammonia level in cirrhotic group was 84.88 µmol/l while it was 28.47 µmol/l in control group. The reference value of normal venous plasma ammonia level used in VITROS AMON slide method is 9 to 33 µmol/l.

When the cirrhotic patients were subgrouped according to size of varices into group 1A (small esophageal varices) and group 1B (medium and large esophageal varices), the mean ammonia concentration in group 1A was 72.00 ± 39.13 µmol/l and in group 1B was 97.75 ± 31.34 µmol/l. Blood ammonia, the newly suggested noninvasive marker of esophageal varices showed significant difference in between small esophageal varices group and medium and large esophageal varices group (p = 0.027) in the present study. Also in Spearman's correlation test, ammonia well correlated with the size of esophageal varices (rho: 0.451, p = 0.004). Degree of correlation found in the present study was comparable with that reported by Tarantino et al in (2009) where rho was 0.43 and p-value was <0.001.

To test the blood ammonia level as a predictor of large varices, sensitivity and specificity of blood ammonia level at different cutoff values were assessed. Blood ammonia at 63 µmol/l had sensitivity of 95% and specificity of 50% in detecting large esophageal varices in patients with cirrhosis. Its PPV was 65.5 µmol/l and NPV was 90.9 µmol/l with accuracy of 72.5%.

Table 1: Correlations of ammonia, platelet count, SLD on USG with size of esophageal varices

Noninvasive markers	*rho*[a]	*p-value*[b]
Ammonia	0.451	0.004*
Platelet	–0.106	0.516
SLD on USG	0.118	0.469

[a]Spearman's rho correlation was done; [b]Significance at p < 0.05

Table 2: Sensitivity, specificity, PPV, NPV and accuracy in percentage at different cutoff values of blood ammonia level (µmol/l) in predicting medium and large esophageal varices

	Cutoff value 63	*Cutoff value 64*	*Cutoff value 65*	*Cutoff value 66*
Sensitivity	95.0	90.0	90.0	85.0
Specificity	50.0	50.0	55.0	55.0
PPV	65.5	64.3	66.7	65.4
NPV	90.9	83.3	84.6	78.6
Accuracy	72.5	70.0	72.5	70.0

PPV: Positive predictive value; NPV: Negative predictive value

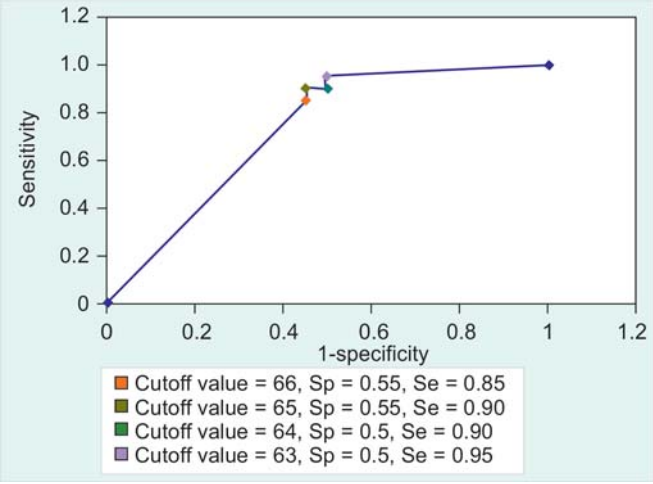

Fig. 1: ROC curve of detection of medium and large varices at different cutoff values of blood ammonia

If cutoff value was raised further, sensitivity declined and specificity increased. In relation to detection of large size varices by means of a noninvasive marker, sensitivity is more important than specificity. So cutoff value 63 μmol/l was found better than other values. The acceptability of noninvasive markers depends mainly on their false negative rate, i.e. those patients with esophageal varices and increased risk of bleeding who are not detected because of exclusion from endoscopic screening. In the present study, the false negative rate was 2.5%, i.e. 1 out of 40 patients would have been missed having large esophageal varices from endoscopic performance if cutoff value of ammonia 63 μmol/l had been used.

Several noninvasive markers were assessed in previous studies. Among them platelet count, SLD on USG were notable. In this series, these two markers were also compared in between the two groups of cirrhosis patients. And they were found to show no significant difference between small esophageal varices and medium and large esophageal group. When Spearman's rho correlation test was done they did not show any correlation with the size of varices (rho: 0.016, p = 0.516; rho: 0.118, p = 0.469 respectively). This finding was in contrast with that found in several cross-sectional studies done by Tarantino,[13] Freeman,[14] Chalasani,[15] Zaman.[16] However, our finding was consistent with the recently published longitudinal study done by the portal hypertension collaborative group of American Association for the Study of Liver Diseases (AASLD) and Qamar.[17]

This study had several limitations. Firstly, the sample size was small. Secondly, 12 out of 40 patients in the study were temporarily on lactulose that might influence their ammonia level. Thirdly, there could be occult GI blood loss. Further large-scale cohort study is recommended to validate these results.

The main observation of the present study was that there was a moderate but significant correlation between blood ammonia level and size of esophageal varices. Blood ammonia at 63 μmol/l had sensitivity of 95% and specificity of 50% in detecting large esophageal varices in patients with cirrhosis. So, it could be a good tool at identifying individuals with large esophageal varices who will need to undergo endoscopy more frequently. Further study with large sample size and prospective cohort studies are needed to validate its efficacy.

REFERENCES

1. Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol 2003;38:266-72.
2. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005;353:2254-61.
3. Cale's P, Desmorat H, Vinel JP, Caucanas JP, Ravaud A, Gerin P, et al. Incidence of large oesophageal varices in patients with cirrhosis: Application to prophylaxis of first bleeding. Gut 1990;31:1298-302.
4. The North Italian endoscopic club for the study and treatment of esophageal varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988; 319: 983-89.
5. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: An evidence-based approach. Semin Liver Dis 1999;19:475-505.
6. de Franchis R. Updating consensus in portal hypertension: Report of the Baveno III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. J Hepatol 2000;33:846-52.
7. D'Amico G, Garcia-Tsao G, Cales P, Escorsell A, Nevens F, Cestari R, et al. Diagnosis of portal hypertension: How and when. In: de Franchis R (Ed). Portal hypertension III. Proceedings of the third Baveno international consensus workshop on definitions, methodology and therapeutic strategies. Oxford, UK: Blackwell Science 2001;36-64.
8. Pagliaro L, D'Amico G, Pasta L, Politi F, Vizzini G, Traina M, et al. Portal hypertension in cirrhosis: Natural history. In: Bosch J, Groszmann RJ (Eds). Portal hypertension. Pathophysiology and treatment. Oxford, UK: Blackwell Scientific 1994;72-92.
9. Garcia-Tsao G, D'Amico G, Abraldes JG, Schepis F, Merli M, Kim WR, et al. Predictive models in portal hypertension. In: de Franchis R (Ed). Portal hypertension IV. Proceedings of the fourth Baveno international consensus workshop on methodology of diagnosis and treatment. Oxford, UK: Blackwell 2006:47-100.
10. D'Amico G, Morabito A. Noninvasive markers of esophageal varices: Another round, not the last. Hepatology 2004;39:30-34.
11. Nicolao F, Efrati C, Masini A, Merli M, Attili AF, Riggio O. Role of determination of partial pressure of ammonia in cirrhotic patients with and without hepatic encephalopathy. J Hepatol 2003;38:441-46.

12. Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med 2003;114:188-93.
13. Tarantino G, Citro V, Esposito P, Giaquinto S, de Leone A, Milan G, et al. Blood ammonia levels in liver cirrhosis: A clue for the presence of portosystemic collateral veins. BMC Gastroenterol 2009;9:21.
14. Freeman JG, Darlow S, Cole AT. Platelet count as a predictor for the presence of oesophageal varices in alcoholic cirrhotic patients. Gastroenterology 1999;116:A1211 (abstract).
15. Chalasani N, Imperiale TF, Ismail A, et al. Predictors of large esophageal varices in patients with cirrhosis. Am J Gastroenterol 1999;94:3285-91.
16. Zaman A, Hapke R, Flora K, et al. Factors predicting the presence of esophageal and gastric varices in patients with advanced liver disease. Am J Gastroenterol 1999;94:3292-96.
17. Qamar AA, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, et al. Platelet count is not a predictor of the presence or development of gastroesophageal varices in cirrhosis. Hepatology 2000;47:153-59.

ABOUT THE AUTHORS

Mohammad Faiz Ahmad Khondaker

General Hospital, Noakhali, Bangladesh

Nooruddin Ahmad

Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Mamun Al-Mahtab (Corresponding Author)

Associate Professor, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, e-mail: shwapnil@agni.com

Sharmin A Sumi

Department of Hepatology, Dhaka Medical College, Dhaka Bangladesh