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Serotonin is a useful non-invasive marker in diagnosis of gastroeosophageal varices in HCV cirrhotic patients

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Abstract:

Oesophageal varices considered a serious consequence of portal hypertension, Serotonin is known as 5-hydroxytryptamine (5-HT) may contribute to maintaining portal hypertension in patients with cirrhosis. Aim of the work: To evaluate the validity of plasma serotonin concentration as a predictor of the presence of esophageal and/or gastric varices in HCV related cirrhosis. Materials and Methods: 100 HCV cirrhotic patients 50 of them with gastroesophageal varices and 50 without, 25 healthy volunteers served as control. All participants were subjected to Lab investigations(CBC, AST & ALT,PT, INR, T and D Bilirubin, a-Fetoprotein, Serum albumin, hepatitis HCV Ab, HBV sAg, HCV RNA, urea and serum creatinine). Child and MELD scores were calculated, upper GI endoscopy for patients, and serum serotonin levels were measured. Results: among 78 were males (78.00%) and 22 were females (22.00%). Among the twenty five healthy volunteers 8 females (32%) &17 males (68%). Mean age for patients was 53.06±7.55while mean age for control group was 41.15±8.18. 38 (76%) of patients were Child A and 12 (24%) were Child B. Ten patients had gastric varices upon endoscopy (20%), eight patients (16%) had Grade I esophageal varices, 25 patients (50%) with Grade

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II, while 18 of them (36%) with Grade III. Patients with varices had higher plasma serotonin level (p-value <0.001). patients with fundal varices had higher plasma serotonin (p-value = 0.02). increased serotonin in those who had grade III varices (p=0.007). (ROC) curve was used to define the best cut off value of the serotonin plasma level which was >30 (ng/ml) with sensitivity of 95%, specificity of 100%, positive predictive value of 100%, negative predictive value of 90.9% with diagnostic accuracy of 98.7%. In conclusion: the high levels of plasma serotonin in HCV cirrhotic patients with portal hypertension and developed varices (specifically fundal varices); may consider serotonin is a useful non-invasive marker for diagnosis and follow up gastroesophageal varices.

Key words: Serotonin, non-invasive marker, diagnosis of gastroeosophageal varices, HCV cirrhotic patients

INTRODUCTION:

Oesophageal varices a serious consequence of portal hypertension, and variceal bleeding occurring in up to 30% of patients with cirrhosis. Although, diagnosis and treatment are improved, a high mortality rate from acute variceal bleeding may still reach up to 20% [1]. All cirrhotic patients without a history of variceal hemorrhage should undergo endoscopic screening to detect presence of varices [2]. However, Endoscopy is a costly, invasive, and time-consuming procedure [3]. Besides, pre-primary prophylaxis is not effective and hampered by side effects. So, non invasive diagnosis of portal hypertension might be useful[4].

Serotonin is known as 5-hydroxytryptamine (5-HT), a biogenic amine that functions as a ligand for a large family of 5-HT receptors. Most of serotonin in the body (90%) is synthesized by entero-chromaffin cells of the gastrointestinal (GI) tract, where it regulates intestinal motility [5]. Serotonin has the ability to regulate hepatic blood flow at both the portal

and sinusoidal levels [6]. Intraportal injections of serotonin were found to significantly increased portal pressure, this suggests that serotonergic mechanisms may contribute to maintaining portal hypertension in patients with cirrhosis [7].

AIM OF WORK:

To evaluate the validity of plasma serotonin concentration as a predictor of the presence of esophageal and/or gastric varices in HCV cirrhotic patients.

MATERIALS AND METHODS:

The study was conducted on 100 patients, diagnosed as HCV related cirrhosis clinically and by imaging, attended the Hepatology outpatient clinic in Ain Shams University Hospitals. Patients were classified as: 50 patients had oesophageal and/or gastric varices (group A), 50 patients without varices (group B), 25 healthy volunteers included as controls. The study protocol was consistent with the ethical guidelines of Helsinki. Written informed consent was obtained from each participant or responsible family members. All participants subjected to full history taking (special emphasis on :blood transfusion, alcohol consumption, previous operations, drugs,…….etc), thorough clinical examination(jaundice ,ascities , pedal edema ,and signs of bleeding tendency……etc). Lab investigations: CBC, AST & ALT,PT, INR, T. and D. Bilirubin, α-Fetoprotein, Serum albumin, hepatitis HCV Ab, HBV sAg, HCV RNA, urea, creatinin).

Child score:

Each patient was then assigned a score and a grade reflecting the severity of his hepatocellular affection, according to the numerical system of modified Child-Pugh classification:

Where CTP Score: 5-6 (Child A), 7-9 (Child B),>10 (Child C)

MELD score:

The MELD score was calculated according to original formula proposed by the mayo clinic group[8]. MELD score =3.8 x log (total bilirubin, mg/dl)+11.2 x log (INR)+9.6 x log (creatinine); we used on-line available worksheet to compute MELD score. (http://www.mayoclinic.org/gi-rst/mayomode15.html).

- Imaging techniques: Pelvi-abdominal ultrasound to determine: liver and spleen size, liver echogenicity, hepatic focal lesions,…..etc).

Upper Gastro-intestinal Endoscopy.

Detection of esophageal and/or gastric varices, and measuring the size, were as the following: Grade I: Straight, pink-bluish veins within the level of the mucosa, diameter≤2 mm. Grade II: Tortuous bluish dilated veins protruding into esophageal lumen diameter 2-3 mm. Grade III: Nodular, tortuous bluish varices, occluding approximately half of the esophageal lumen, diameter 3-4mm.Grade IV: Grape-like, blue vascular convolutes protruding far into the esophageal lumen. The esophageal lumen becomes visible only after insufflations of air. Fine angiectasias are present on the surface of the vessels (varix on varix) and pinpoint thinning of epithelium (cherry-red-spots) [9].

For Fundal varices Sarin classification was used that is based on the anatomic location of varices and their relation to esophageal varices. According to this classification; gastric varices are divided into two types: gastroesophageal varices (GOV) and isolated gastric varices (IGV) [10].

Measurement of plasma serotonin by ELISA:

Using Serotonin ELISA Assay Kit (Eagle BioSciences) More than 98% of the circulating serotonin is located in the platelets

and is releases during blood clotting .Blood collected by veni-puncture into plastic tubes containing EDTA or citrate as anticoagulant. Samples are kept and centrifuged at room temperature for 10 min at200 x g to obtain platelet-rich plasma (PRP).An aliquot of PRP is centrifuged at 4500 x g for 10 min at 4°C to obtain platelet- free plasma (PFP).

Calculation of results:

On a semi logarithmic graph paper the concentration of the standards are plotted against their corresponding OD (optical density) (ordinate, linear). Alternatively, the optical density of each standards and sample can be related to the optical density of the zero standard, expressed as the ratio OD/OD max, and then plotted on the ordinate.

The concentration of the samples can be read directly from this standard curve by using the average optical density.

Reference Values (Normal):

Plasma (platelet-free): < 10 ng/ml

Serum: Female 80 - 450 ng/ml

Male 40 - 400 ng/ml [11]

Serotonin (ng/ml) x 5.67 = nmol/l.

STATISTICAL ANALYSIS:

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0.Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done: Independent-samples t-test of significance was used when comparing between two means. Chi-square (X2) test of significance was used in order to compare proportions between two qualitative parameters. Pearson's correlation coefficient (r) test was used for correlating

data. ROC-curve: Receiver Operating Characteristic curve analysis

Sensitivity: probability that the test results will be positive when the disease is present (true positive rate, expressed as a percentage). Specificity: probability that the test results will be negative when the disease is absent (true negative rate, expressed as a percentage). PPV: Positive Predictive Value (probability that the disease is present when the test is positive). NPV: Negative Predictive Value (probability that the disease is present when the test is negative). Accuracy: the ratio of the true positive and true negative on all patient. P-value <0.05 was considered significant, P-value <0.001 was considered as highly significant and P-value >0.05 was considered insignificant.

RESULTS:

The data collected revealed that: eighty patients 78 were males (78.00%) and 22 were females (22.00%). Among the twenty five healthy volunteers 8 females (32%) &17 males (68%). Mean age for patients was 53.06±7.55while mean age for control group was 41.15±8.18. 38 (76%) of patients were Child A and 12 (24%) were Child B. Ten patients had gastric varices upon endoscopy (20%), eight patients (16%) had Grade I esophageal varices , 25 patients (50%) with Grade II, while 18 of them (36%) with Grade III.

Table (1): Comparison between group I and group II as regard laboratory data.

	Group I		Group II		Control		LSD		
	Mean	±SD	Mean	±SD	Mean	±SD	I vs. II	I vs. III	II vs. III
Hb gm/dl	11.41	1.60	12.22	1.44	12.44	1.37	**0.020**	**0.018**	0.586
Plt/mm^3	118.95	57.32	157.33	70.72	272.75	59.29	**0.010**	**<0.001**	**<0.001**
WBCs / mm^3	5460.00	1738.04	5600.00	1758.20	6232.50	1722.47	0.721	0.109	0.191
SGOT IU / L	60.73	20.89	77.80	23.96	20.90	10.50	**<0.001**	**<0.001**	**<0.001**
SGPT IU / L	50.88	14.85	73.40	20.24	22.20	10.62	**<0.001**	**<0.001**	**<0.001**
ALKP	61.30	16.23	62.45	18.84	65.20	12.58	0.771	0.351	0.558
Bil. T mg / dl	1.76	2.49	1.15	0.40	0.85	0.32	0.132	0.109	**0.004**
Bil. D mg / dl	1.17	2.35	0.68	0.27	0.36	0.20	0.194	0.130	**<0.001**
S. Alb g/dl	3.63	0.50	4.33	0.37	4.45	0.59	**<0.001**	**<0.001**	0.340
PT second	16.18	2.86	13.75	1.21	12.54	0.70	**<0.001**	**<0.001**	**<0.001**

PTT second	47.80	11.36	27.38	1.53	25.80	0.77	**<0.001**	**<0.001**	**<0.001**
INR %	1.30	0.22	1.13	0.10	1.05	0.05	**<0.001**	**<0.001**	**<0.001**
S. Creat mg /dl	1.07	0.32	0.92	0.22	0.85	0.22	**0.015**	**0.007**	0.231

Patients with varices had lower platelet count, serum Alb. and higher INR, BIL D as compared to other groups (p-value <0.001).

Table (2): Serotonin plasma level in different groups.

	Group I		Group II		Control		LSD		
	Mean	±SD	Mean	±SD	Mean	±SD	I vs. II	I vs. III	II vs. III
Serotonin Plasma Level	158.20	68.52	71.05	59.58	12.80	9.20	<0.001	<0.001	<0.001

Patients with varices had statistically significant higher plasma serotonin level as compared to patients without varices and control groups, p-value <0.001.

Table (3): Comparison between fundal and non fundal varices as regard serotonin plasma level in group I.

Type	**Sertonine Plasma Level**		**t-test**	
	Mean	**±SD**	**t**	**p-value**
Fundal	207.88	60.28	5.919	**0.020**
Non fundal	145.78	65.49		

A significant increase in serotonin plasma level in patients with fundal varices compared to those with non-fundal varices (p=0.020).

Table (4): Serotonin plasma level according to the grade of varices in group I.

	Serotonin Plasma Level				ANOVA test	
	Mean	±SD	Min.	Max.	F	p-value
Grade I	147.90	74.95	15.00	230.00	4.396	0.007 (S)
Grade II	155.75	72.39	15.00	240.00		
Grade III	176.64	58.17	60.00	240.00		
Fundal	227.17	7.40	220.00	240.00		

This table showed that free plasma serotonin level was higher in group with fundal varices as compared with those with esophageal varices and was higher in those with Grade III as compared with those with Grade II, I (p-value 0.007).

Table (5): Comparison between Child classification as regard serotonin plasma level in patients with varices.

Child	Serotonin Plasma Level		t-test	
	Mean	±SD	t	p-value
A	157.33	69.06	0.019	0.892
B	160.80	70.46		

No significant difference between child classification as regard serotonin plasma level in patients with varices with p-value 0.892.

Table (6): Correlation between serotonin plasma level and other parameters in the group of patients with varices.

Group I	Serotonin Plasma Level	
	r	p-value
Age (years)	0.081	0.620
Hb	-0.051	0.756
Plt	-0.316	0.050
WBCs	0.043	0.790
SGOT	0.069	0.674
SGPT	0.134	0.409
ALKP	-0.210	0.194
Bil. T	-0.002	0.989
Bil. D	-0.015	0.926
S. Alb	-0.065	0.688
PT	0.173	0.286
PTT	0.072	0.657
INR	0.128	0.430
S. Creat	0.427	0.006
Urea	0.165	0.308
Liver	0.398	0.255
Spleen	0.110	0.763
PVD	-0.072	0.660
AFP	-0.044	0.789
MELD	0.291	0.068

This table showed negative correlation between serotonin plasma level and Platelets and S. Creatinin in patients group with varices.

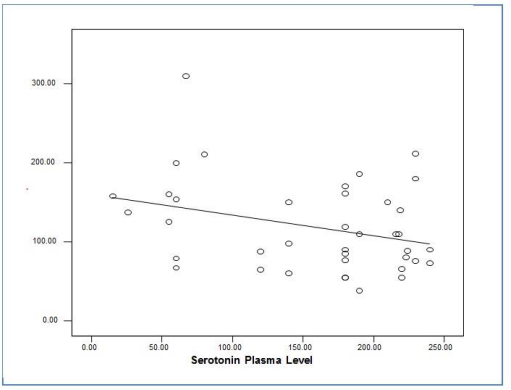

Fig. (1): Negative correlation and significant between Plt. And serotonin plasma level.

Table (7): Correlation between serotonin plasma level and MELD score, grade of varices in patient group.

Group I	Serotonin Plasma Level	
	r	p-value
MELD	0.291	0.068
Grade of Varices	0.307	0.036

This table showed that there was positive correlation between The grade of varices and serotonin plasma level (p-value 0.036), and no correlation between MELD score and grade of varices (p =0.68).

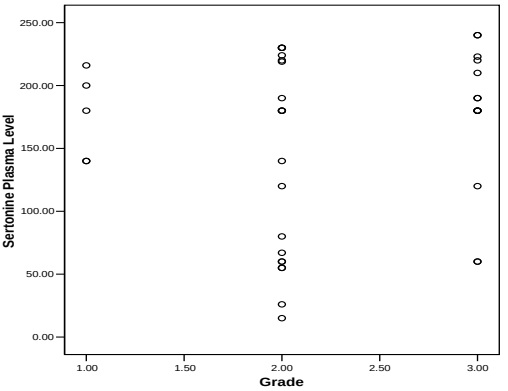

Fig. (2): Positive correlation and significant between plasma serotonin level and grade of esophageal varices.

Table (8): Diagnostic validity test for patients and control group as regard serotonin plasma level.

Cut-off	Sens.	Spec.	+PV	-PV	AUC
>30	95%	100%	100%	90.9%	98.7%

Receiver operating characteristics (ROC) curve was used to define the best cut off value of the serotonin plasma level which was >30 (ng/ml) with sensitivity of 95%, specificity of 100%, positive predictive value of 100%, negative predictive value of 90.9% with diagnostic accuracy of 98.7%.

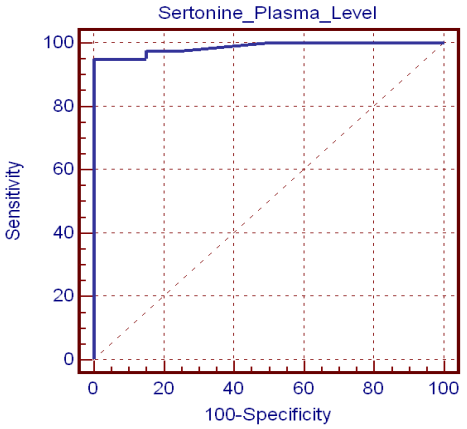

Fig. (3): ROC curve between patients with varices and control as regard serotonin plasma level.

DISCUSSION:

It would be impossible to perform endoscopic examinations at regular interval for all patients with chronic liver disease and it may be more cost-effective to routinely screen only, cirrhotic patients at high risk on the other hand, refuse repeated endoscopies because of discomfort endoscopic examination which considered an invasive procedure [12].

Several non-invasive tools have been evaluated in the search of alternatives to endoscopy. Such tools include clinical/laboratory parameters and abdominal ultrasound with or without Doppler quantitative studies [13].

According to the laboratory data in the present study a lower platelet count, serum Alb. and higher INR, D. Bil prevalent with the presence of varices. This in agreement with ***Schepke et al. (2001)*** and ***Madhotra et al. (2002)*** that low serum albumin level and prolonged prothrombin time and increased direct bilirubin were significantly increased with the presence of varices [14,15].

Furthermore, platelets count was lower in the patients with varices which agrees with the results of ***Zaman et al.***

(2001) and ***Schepke et al. (2001)*** [16,14]. The mean platelets count in patients with varices was (118.95x 103/µL), which was higher than ***Zaman et al. (2001)*** and ***Schepke et al. (2001)*** [15,13]; who reported a mean platelets count of (≤ 90 x103/µL) and < 100 x 103/µL respectively. Their lower mean platelets count may be attributed to the high percentage of alcoholic cirrhosis patients included in these studies (44%), it has been reported that alcohol has a myelotoxic effect on the bone marrow [17].

When the free plasma serotonin level was investigated, it was noticed that the levels of free serotonin were higher in patients with liver cirrhosis than in healthy subjects ($p<0.001$) ***Culafic DM et al. 2007***, studied plasma serotonin level and platelet serotonin content in 30 patients with liver cirrhosis versus 30 controls, they found the mean plasma serotonin level was higher in liver cirrhosis patients than in healthy subjects (215.0 +/- 26.1 vs 63.1 +/- 18.1 nmol/L; $P < 0.0001$) [19]. This was in agreement with the results of the present study.

A study performed by ***Rudić JS et al. 2010*** in which free serotonin levels were investigated and the levels of free serotonin were also higher in patients with liver cirrhosis than in healthy subjects[19].

In the present study, there was no significant difference between different grades of child classification as regard serotonin plasma levels in patients with varices (p-value 0.892). This was against ***Culafic DM et al. 2007***, who found the plasma serotonin levels were significantly higher in Child-Pugh grade A/B than in grade C patients (246.8 +/- 35.0 vs 132.3 +/- 30.7 nmol/L; $P < 0.05$) [18].

On the other hand, ***Rudić JS et al., 2010*** met with our results that plasma serotonin levels were higher in patients with liver cirrhosis than in healthy subjects and there was significant correlation between the free plasma serotonin level and Child score [19].

Moreover, the current study represented a higher levels of free serotonin in those with esophageal and/or fundal than the patients without varices detected. The level of free plasma serotonin was related the grade of esophageal varices and was higher in those having fundal varices than the non fundal group (p = 0.02).

Abdelkader et al. 2015, studied 60 patients with liver cirrhosis, 30 had gastroesophageal varices and 30 without, and 30 control. They found a higher serotonin level in patients with liver cirrhosis specifically those having varices than control. There was highly significant difference in plasma free serotonin levels in patients with esophageal and gastric varices compared with those with esophageal varices alone [20].

Also, there was a positive correlation between The grade of varices and serotonin plasma level with (p-value 0.036). ***Abdelkader et al. 2015*** found A highly significant stepwise progressive increase in the marker level was recorded through grades of oesophageal varices from grade 2 to grade 5 (grade 2, 20.7±7.7 ng/ml; grade 3, 44.3±8.9 ng/ml, P<0.01; grade 4, 100.1±12.4 ng/ml, P<0.01; grade 5, 114.6±14.7 ng/ml, P<0.05) [20].

On the contrary, these results disagree with ***Rudić JS et al., 2010*** that the free plasma serotonin had no correlation with the grade of the esophageal varices this may be due to difference in sample size [19].

When we studied the diagnostic validity of plasma serotonin levels we used the Receiver operating characteristics (ROC) curve was used to define the best cut off value of the serotonin plasma level which was >30 (ng/ml) with sensitivity of 95%, specificity of 100%, positive predictive value of 100%, negative predictive value of 90.9% with diagnostic accuracy of 98.7%.

Abdelkader et al. 2015, found a serotonin cutoff value of 24 ng/ml was chosen, with 100% sensitivity, 96.7%

specificity, 98.3 to discriminate all chronic liver disease patients from healthy controls (area under the curve=0.981). A cutoff value of 58.0 ng/ml to differentiate between patients with and without esophageal varices, with 80% sensitivity and 86.7% specificity (area under the curve=0.855). this difference in results may be due to a higher sample size in the present study [20].

The study of ***Nevens et al., 1991*** investigated the effects of ritanserin, a selective S2-serotonergic antagonist, in portal-hypertensive rats whose condition was due to partial portal vein ligation. The animals were randomized under double-blind conditions into two groups: the first received ritanserin (0.7 mg/kg body wt, intravenously), and the second received the same volume of placebo (isotonic saline solution). Ritanserin administration significantly reduced portal pressure (from 11.8 +/- 0.8 mm Hg to 9.4 +/- 0.6 mm Hg; p less than 0.05). This was associated with lower porto-collateral resistance (1.8 +/- 0.2 mm Hg/ml/min 100 gm in the ritanserin group vs. 2.3 +/- 0.2 mm Hg/ml/min 100 gm in rats receiving placebo; not significant), but they saw no changes in portal-vein inflow (5.5 +/- 0.7 ml/min 100 gm vs. 5.4 +/- 0.5 ml/min 100 gm), mean arterial pressure (95.9 +/- 3.5 mm Hg vs. 94.0 +/- 4.0 mm Hg) and cardiac index (31.9 +/- 3.5 ml/min 100 gm vs. 28.5 +/- 2.6ml/min100gm) [21].

Hepatic arterial and kidney blood flows were not modified by ritanserin. In summary, their results demonstrated that ritanserin infusion decreases portal pressure without causing systemic hemodynamic changes. This effect is probably due to a decrease in portocollateral resistance in portal-hypertensive rats. These results provide further for a role of serotonin in thepathogenesis of portal hypertension [21].

Concentration of circulating serotonin in liver cirrhosis can be influenced by other factors, such as altered serotonin catabolism due to an elevated activity of monoamino oxidase

and impaired metabolism of tryptophan, as serotonin precursor. Impaired metabolic function in liver cirrhosis contributes to elevated plasma serotonin. Moreover, vasoactive substances, produced in the splanchnic circulation, bypass the liver in the presence of porto-systemic collaterals and directly enter the systemic circulation [22].

According to the presented data, serotonin has a role in development of portal hypertension and subsequently oesophageal and gastric varices. In the current study a higher plasma serotonin levels reported in patients with liver cirrhosis specially who had varices, specifically with fundal varices, had an increased levels than oesophageal, so, serotonin level can expect the severity of the developing varices.

In conclusion: the high levels of plasma serotonin in HCV cirrhotic patients with portal hypertension and developed varices (specifically fundal varices); may consider serotonin is a useful non-invasive marker for diagnosis and follow up gastroesophageal varices.

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