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A Clinical Study of Cardiovascular Dysfunction in Patients of Cirrhosis of Liver.

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ABSTRACT

Background: Cirrhosis is a very common ailment in India mostly caused by alcoholism, viral hepatitis and malnutrition. The clinical picture of patients with cirrhosis is dominated by the classical complications such as ascites, bleeding from esophageal varices, portal hypertension and encephalopathy. Cardiovascular abnormalities have been reported by several investigators. **Methods:** It is a cross sectional study done on 60 patients admitted to NIMS Medical College, Jaipur between Jan. 2013 to Dec. 2014. USG of liver was done by GE Voluson promachine with probe frequency of 3.5 MHz and high frequency of 7-10 MHz for detection of cirrhosis and ascites with special reference to caudate lobe, portal vein and spleen. ANOVA with post hocTukey HSD was used for analysis of continuous variables whereas Chi-square test was used for nominal/ categorical variables. p value < 0.05 was taken as significant. **Results:** Diastolic dysfunction is measured by E/A ratio was prevalent LVED diameter, IV septal thickness, left ventricular posterior wall thickness were proportional to severity of liver cirrhosis. Electro physiologically, 38.33% patients of cirrhotic liver patients had prolonged QTc interval. Here, as far as cardiac abnormality were considered, we found QTc prolongation more in severe degree of cirrhosis MELD score III (7 out of 10) 70%, than moderate (40%) MELD score II and mild (20%) MELD score I of cardiac QTc prolongation. **Conclusion:** Diastolic dysfunction is a major criteria of cirrhotic cardiomyopathy which can be diagnosed by electro and echo cardiography.

Keywords: Cardiovascular, Cardiomyopathy, Cirrhosis, Diastolic dysfunction.

INTRODUCTION

Cardiomyopathy is derived from the Greek roots: cardio (heart) + mys (muscle) + pathos (disease), that is, it is a condition affecting the heart muscles. In 2005, a working party of expert hepatologists and cardiologists met at the World Congress of Gastroenterology and proposed a working definition of cirrhotic cardiomyopathy which states that "cirrhotic cardiomyopathy is a form of chronic cardiac dysfunction in patients with cirrhosis, characterized by blunted contractile responsiveness to stress, and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease." Cirrhosis is a very common ailment in India mostly caused by alcoholism, viral hepatitis and malnutrition. The clinical picture of patients with cirrhosis is dominated by the classical complications such as ascites, bleeding from esophageal varices, portal hypertension and encephalopathy.[1]

Cardiovascular abnormalities have been reported by several investigators. Systemic hemodynamic changes occur in cirrhotic patients.

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There is hyperdynamic circulatory state, decreased arterial blood pressure, decreased peripheral resistance, and increased cardiac output. Because of reduced systemic vascular resistance and increased arterial compliance, left ventricular failure may be latent in cirrhosis. Impaired ventricular function become manifest under strain or treatment with vasoconstrictors. This type of cardiac dysfunction has been termed as cirrhotic cardiomyopathy.[2,3]

Three major pathophysiologic abnormalities are observed: cardiac electrophysiological abnormalities, structural and functional ventricular abnormalities, and abnormal ventricular response in presence of pharmacologic, physiologic, or surgical stress.[4]

Cirrhotic patients have hyperdynamic circulation with decreased peripheral vascular resistance, increased cardiac output and stroke volume, increased organ blood flow, low systemic arterial pressure, and decreased arterio-venous oxygen difference. The level of circulating vasoactive substances which are not inactivated by liver is increased such as vasoactive intestinal peptide, glucagon, and tumor necrosis factor-α, prostacyclin, nitric oxide, endothelin-1, and endothelin-3.[1-3]

Cirrhotic cardiomyopathy was initially thought to be of little clinical relevance. However, with the frequent use of invasive procedures like surgical porto-caval shunts, transjugular intrahepatic porto-systemic shunt and liver transplantation, the adverse consequences of cardiac dysfunction became evident. These procedures put additional stress on the dysfunctional heart, precipitating overt cardiac failure. However, there is still a great deal about cirrhotic cardiomyopathy that is unknown.[5] We do not yet have a single diagnostic test that can identify patients with cirrhotic cardiomyopathy. Cirrhotic Cardiomyopathy may be a major cause of morbidity

and mortality in patients with cirrhosis and liver transplant patients. With the advent of increased liver transplantation in India, this entity may have its impact on the transplantation success.

The aim of the study is to know the incidence of cardiomyopathy in patients of cirrhosis of liver, irrespective of etiology. To establish correlation between severity of cirrhosis and incidence of cardiomyopathy.

MATERIALS AND METHODS

It is a cross sectional and observational study done on 60 patients admitted to NIMS Medical College, Jaipur between Jan. 2013 to Dec. 2014 with following criteria:

(a) Inclusion criteria: (i) Age group > 18 years, (ii) Patients with clinical features and laboratory tests suggestive of cirrhosis of liver (including ultrasonography).

(b) Exclusion criteria: (i) Patients suspected of malignancy of liver (ii) Patients of IHD/Valvular heart disease, conduction defects, cardiac arrhythmias and congenital heart defects (iii) Known cases of diabetes and hypertension (iv) Hepatic encephalopathy (v) Patients having cQTC interval prolongation.

Sample size was calculated at 95% confidence level assuming standard deviation of 5 in MELD score as observed in the study of Silvestre OM et al.[1] At the precision (absolute allowable error) of 1.3, minimum 60 patients of cirrhosis of liver were required as sample size.

The study was approved by institutional scientific and ethics committee. The study was not funded by any government body or any company. There is no conflict of interest, if at all with any.

USG of liver was done by GE Voluson promachine with probe frequency of 3.5 MHz and high frequency of 7-10 MHz for detection of cirrhosis and ascites with special reference to caudate lobe, portal vein and spleen.

12 lead ECG was done to calculate QT interval manually, and corrected QT (QTC) by using Bazett's formula as

$$QTC = \frac{QT\ \ Interval}{\sqrt{RR}\ \ Interval}$$

Prolonged QT interval was defined as value > 440 m sec (0.44 sec). 2D Echo were done by Philips HD (7 × E) with adult probe, and was used to assess cardiac anomaly with special reference to left atrial diameters left ventricle end diastolic volume, I.V. septal thickness, left ventricular posterior wall thickness and to assess E/A ratio where E stands for early maximum left ventricular filling velocity, and A for late diastolic left ventricle filling velocity; left ventricle systolic function was calculated using ejection fraction (EF %) and diastolic function was assessed by E/A and if ratio was < 1, it was taken as diastolic dysfunction.

Lt. ventricular mass was calculated by ASE-cube formula:

Lt. ventricle mass (in gms) = 0.8 {1.04 [([LVEDd + I VSd + PWs]^3 - LVEDd^3)]} + 0.6

Here LVEDd stands for Left ventricle end diastolic diameter in mm.

PWd = for posterior left ventricular wall thickness at end diastole (in mm)

I VSd = for septal wall thickness at end diastole (in mm)

1.04 = Sp gravity of the myocardium (g / cm^3)

Normal left ventricular mass in males is < 170 gm and in females it is < 160 gm

Lt. ventricular mass index was calculated as Lt. ventricular mass for body surface area.

Cirrhotic cardiomyopathy was declared by features found in those patients having:

(a) Diastolic heart failure sp. prolongation of QT interval

(b) E/A ratio < 1 (corrected QTC - > 0.44 sec)

(c) Increased wall thickness with LVEF > 50% and without structural lesions were labelled as cirrhotic cardiomyopathy.

Patients grading for cirrhosis was done by MELD criteria (MELD stands for Model for End Stage Liver Disease)

MELD = 3.78 [Ln Serum bilirubin (mg/dL)] + 11.2 [Ln INR] + 9.57 [Ln serum creatinine (mg/dL)] + 6.43

MELD Scoring: Stage I MELD Score $\leq$ 9
Stage II MELD Score 10-19
Stage III MELD Score $\geq$ 20

Statistical analysis: Continuous variables were summarized as mean and standard deviation while nominal / categorical variables as proportions (%). ANOVA with post hoc Tukey HSD was used for analysis of continuous variables whereas Chi-square test was used for nominal/ categorical variables. p value < 0.05 was taken as significant.

Medcalc 14.0.0 version software was used for all statistical calculation. Microsoft Word and Excel was used to generate graphs, tables and derivation.

RESULTS

In the present study, most of the patient's i.e 70% (42/60) were in age group of 40-60 years, 26.66% above 60 years and 3.33% (2/60) were below 40 years of age. Minimum age was 37 years and maximum age was 72 years with the mean age 55.82 ± 7.44 years. Genovesi et al[2] showed in their study that most of the patients were >45 years of age (86.1%), with the majority being in the 45 - 60 year age group (51.2%).

Sex distribution: 41 out of 60 were males (68.33%) in contrast to 19 (31.67%) were females.

Biochemistry: Mean serum creatinine in MELD Gr. I was 0.80 ± 0.15 mg/dl, 1.31 ± 0.13 mg/dL in

MELD gr. II and 1.78 ± 0.16 mg/dl in MELD group III thereby concluding that if more is the MELD Score, higher will be the serum creatinine level.

Serum bilirubin levels: Mean serum bilirubin level in MELD gr I was 1.19 ± 0.13 mg/dL, in MELD group II it is 2.36 ± 0.4 mg/dL and in MELD group III it is 7.22 ± 13.7 mg/dL inferring thereby a significant difference in S. bilirubin levels in each MELD groups (p<0.001).

In prospect of MELD Score, more severe is the degree of liver cirrhosis, higher were the levels of S. creatinine, Serum bilirubin and INR levels [Table 1].

Liver Enzymes (SGOT/SGPT): In our study values of SGOT in respect to MELD scoring group were : in MELD group I - 64.58 ± 2.10 U/L, MELD II was 75.35 ± 2.10 U/L and MELD group III were 80.47 ± 2.91 U/L meaning thereby that higher is the MELD scoring, more was the SGOT levels. Similarly SGPT levels were in MELD group I, SGPT was 56.37 ± 1.76 IU/L, MELD group II, SGPT was 62.19 ± 2.77 IU/L and MELD group III, SGPT levels were 60.90 ± 1.58 IU/L concluding thereby that more severe is the degree of cirrhosis, higher were the liver enzyme levels (p <0.001

Table 1: Comparison of MELD groups with respect to serum total bilirubin.

Parameter	MELD Group	No.of Patients (n)	Mean serum. Bilirubin (mg/dl)	Standard. Deviation	ANOVA		'p'<0.05 from*
					'F'Ratio	'p'Value	
Serum Bilirubin	1	20	1.19	0.13	332.18	<0.001	2,3
	2	30	2.36	0.40			1,3
	3	10	7.22	1.37			1,2

*Tukey HSD

Cardiac Parameters in relation to cirrhosis: The findings of QTc interval as inferred by ECG in MELD group 3 (458.53 ± 22.83 m sec) was significantly higher (p<0.001) in comparison to mean QTc interval in MELD group I (407.38 ± 21.65 sec) and MELD group II (439.03 ± 11.80 m sec). As far as prolongation of QTc is concerned it is 70% (7/10) in group III, 40% (12/30) in group II and 20% (4/20) in group I of MELD score suggesting thereby that there is a positive correlation between degree of cirrhosis and prevalence of QTc prolongation. Overall on an average, QTc prolongation was seen in 38.33% (23 out of 60) patients of cirrhosis. Similarly, frequency of QTc prolongation was found to be 46.2% in the study done by Bernardi et al[3] irrespective of etiology of cirrhosis. Koser et al[4] demonstrated frequency of QTc prolongation of 32% in study population. Also in a study by Li et al[5] QTc prolongation was seen in 46.93% patients [Table 2].

Table 2: Comparison of MELD Groups with Respect to QTc Interval

Parameter	MELD Group	No.of Patients (n)	Mean QTc (m sec)	Standard. Deviation	ANOVA		'p'<0.05 from*
					'F' Ratio	'p' Value	
QTc	1	20	407.38	21.65	33.38	<0.001	2,3
	2	30	439.03	11.80			1,3
	3	10	458.53	22.83			1,2

*Tukey HSD

Diastolic Dysfunction: E/A ratio which is a marker of diastolic dysfunction, was found to be abnormal in 48.33% (29/60) patients in present study, varying from 70% (7 out of 10) in gr. III MELD Group and 50% (10/20) MELD group I depicting a positive correlation between severity of cirrhosis and E/A ratio degree which is a hall mark of ventricular dysfunction (rho =-0.538, p <0.001).

A study done by Achecar and A. Gonzalec-Tallon[6], in 2011 showed that 50% of cirrhotic patients had left ventricular diastolic dysfunction. Prevalence of diastolic dysfunction was 51% in a study done by A. Salari, A. Shafaghi, M. Ofoghi, A. Saeidinia and F. Mansour-Ghanaeiin in 2013.[7]

A study carried out by G. M. A. Nasr, M. M. Eldin, and M. Ragheb showed that 80%, 25%, and 24% of diastolic dysfunction were present in patients who had severe, moderate, and mild liver fibrosis, respectively.[8]

Cardiac Structural Abnormality: Mean left atrial diameter in MELD group 2 (37.09 ± 4.20 mm) and group 3 (37.82 ± 3.98 mm) were higher than MELD Score 1 (33.81 ± 2.41 mm) which is statistically important (p = 0.004).

Similar observations persisted for left ventricular end diastolic diameter which varied from 48.28±3.58 mm in MELD group I to 52.39±4.03 mm in MELD group III (p = 0.038) thereby inferring that higher is the degree of MELD score, worse is the left ventricular diastolic dysfunction.

Similar were the findings of inter-ventricular septal wall thickness which was higher in MELD score III (9.55 ± 2.24 mm) than in MELD score I (8.07 ± 1.30 mm) and 8.71 ± 0.86 mm in MELD Score II. Various other studies also support our findings.[1,6]

DISCUSSION

The left ventricular mass index as calculated by left ventricular mass/SQ meter of body surface area varied from 86.30±17.46 gm m^2 in MELD group I

and 112.40 ± 24.78 gm/m^2 in MELD group III inferring thereby a proportional increase in left ventricular mass index in relation to degree of severity of cirrhosis (p = 0.002). Similar results were demonstrated in a study.[1]

In study done by Pozzi et al[9], in patients of cirrhosis with and without ascites left ventricle wall thickness was increased (18.6 ± 0.6 and 20.1 ± 0.8 vs. 17.2 ± 0.7, $P < 0.05$ and $P < 0.01$, respectively), irrespective of the post-viral or alcoholic cause of liver disease. In a study performed by Fu-Rong Sun et al[10] in 2011, of 82 patients, MELD score was positively correlated with enlarged left atrial diameter, increased inter-ventricular septum thickness (IVST). Ejection fraction at rest was normal in all the three MELD groups with no significant difference (p =0.648). In a study by Wong et al[11], mean ejection fraction was 62.7±3.6 % and 63.4±2.8 % in study of Pozzi et al[9] which was similar to our study.

According to the above mentioned criteria, cardiomyopathy was present in 29 patients out of 60 patients (48.33%). In MELD group 1 incidence of cardiomyopathy was 50% (10/20); in group 2 it was 40 % (12/30) and in group 3 it was 70% (7/10) which showed that incidence of cardiomyopathy increases with increase in the severity of liver cirrhosis.

In a study done in 2013, among the 231 patients with cirrhosis, 118 (51.1%) met criteria for Cirrhotic Cardiomyopathy.[12] The results of our study were similar to a study by Sajid N[13], Lahore. Cirrhotic cardiomyopathy was observed in 49% of patients with liver cirrhosis.

CONCLUSIONS

Diastolic dysfunction, which is a major criteria of cirrhotic cardiomyopathy as measured by E/A ratio was prevalent LVED diameter, IV septal thickness, left ventricular posterior wall thickness were proportional to severity of liver cirrhosis.

Electro physiologically, 38.33% patients of cirrhotic liver patients had prolonged QTc interval.

Here, as far as cardiac abnormality were considered, we found QTc prolongation more in severe degree of cirrhosis MELD score III (7 out of 10) 70%, than moderate (40%) MELD score II and mild (20%) MELD score I of cardiac QTc prolongation.

RECOMMENDATIONS

Early detection of systolic / diastolic myocardial dysfunction by 2D Echo and appropriate early treatment of this cirrhosis will delay the onset of cardiomyopathy.

A high alerting social awareness programed to promote alcoholic withdrawal and nutritional supplementary drive to overcome hepatic assault will minimize cirrhosis and thereby decreasing the incidence of cardiomyopathy and national burden on economy of nation. More acute interventional cardiac studies may be promoted for early detection of cardiomyopathy secondary to cirrhosis and measures to lessen the vulnerability to hepatic insult due to cardiac dysfunction by early diagnosis by way of TNF, NFK for the detection of cardiomyopathy.

REFERENCES

1. Silvestre OM. QT interval prolongation. Annals of Hepatology 2013;12(1):85-91.
2. Genovesi S. QT interval prolongation and decreased heart rate variability in cirrhotic patients. Cli Sci (Lond) 2009;116(12):851-9.
3. Bernardi M, Calandra S, Colantoni A. Q-T interval prolongation in cirrhosis: Prevalence, relationship with severity, and etiology of the disease and possible pathogenic factors. Hepatology 1998;27:28-34.
4. Kosar F, Ates F, Sahin I, Karincaoglu M, Yildirim B. QT interval analysis in patients with chronic liver disease: a prospective study. Angiology 2007;58:218–24.
5. Li, L., Liu, HR., Shu, JL. Clinical Investigation of Q-T Prolongation in Hepatic Cirrhosis. Zhonghua Yi XueZaZhi 2007;87:2717-8.
6. Achecar L, Gonzalec-Tallon A, Relationship between circulatory dysfunction and severity of cardiomyopathy in patients with cirrhosis, in Proceedings of the 46th Annual Meeting of the European Association for the Study of the Liver (EASL 11), 2011.
7. Salari A. Clinical Study Diastolic Dysfunction and Severity of Cirrhosis in Nonalcoholic Cirrhotic Patients. International Journal of Hepatology 2013;21:56-9.
8. Nasr GM, Eldin MM, Ragheb M. Systolic and diastolic functions, QT interval and myocardial perfusion imaging in post-viral cirrhosis with and without ascites. HeartMirror Journal 2008;2(1):28–35.
9. Pozzi M, Carugo S, Boari G, Pecci V, de Ceglia S, Maggiolini S. Functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. Hepatology 1997;26:1131–7.
10. Sun FR, Wang Y, Wang BY, Tong J, Zhang D, Chang B Relationship between model for end-stage liver disease score and left ventricular function in patients with end-stage liver disease HepatobiliaryPancreat Dis Int 2011;10:50-4.
11. Wong F, Liu P, Lilly L, Bomzon A, Blendis L. The role of cardiac structural and functional abnormalities in the pathogenesis of hyper-dynamic circulation and renal sodium retention in cirrhosis. Clin Sci 1999;97:259–67.
12. Belay T, Gress T, Sayyed R. Cirrhotic cardiomyopathy among patients with liver cirrhosis. Open Journal of Gastroenterology 2013;3:344-8.
13. Nisar S, Qazi S, Ashraf Y. To Assess the Frequency of Cirrhotic Cardiomyopathy among Patients with Cirrhosis of Liver. Open Journal of Gastroenterology 2012;21:35-9.

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