Original Article

To Study the Relationship of Caffeine Elimination and Child's Pugh Classification in Groups of Patients with Liver Cirrhosis

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ABSTRACT

Background: Serum Caffeine clearance determination is a useful method to evaluate the severity of liver disease and predict short-term survival of cirrhotic patients. Caffeine concentrations correlated well with the score indicating the sufficiency of the organ according to Child- Turcotte classification score. It offers another choice for the quantitative measurement of liver functional reservoir.

Objectives: Study is designed to find out the relationship of Caffeine elimination and Child's classification in groups of patients with liver cirrhosis.

Study Design: Cross sectional Study.

Place and Duration of Study: The study was conducted at the Medical Ward of Services Hospital Lahore from July 2004 to December 2004.

Material and Methods: Forty patients with liver cirrhosis with age range 40-55 years and 20 aged matched normal healthy volunteers were enrolled in this study. Patients were taken from the medical ward of Services Hospital Lahore. After an overnight fast, the first blood sample was collected at 8 a.m., immediately followed by an oral administration of 200 mg Caffeine. Subsequent samples of venous blood were obtained at 8.30 a.m., 9 a.m., 11 a.m., 2 p.m. and 5 p.m. The Caffeine clearance was determined by reversed-phase high pressure liquid chromatography using a Phenomenex Gemini C18 column using a wavelength of 273 nm.

Results: (Jaundice presented with highest frequency distribution and percentages. This was followed with ascities, edema, family history of hepatitis/jaundice and anemia. Ultrasonographic findings showed that in 50% of the patients. Other 50% of patients have normal and shrunken liver).

Caffeine concentration in child class A was significantly decreased at base line ($P<0.001$), 3 hours ($P<0.05$), 6 hour ($P<0.001$) and 9 hour ($P<0.001$) as compared to the controls. In child class B the Caffeine concentration was significantly decreased at base line ($P<0.001$), 3 hours ($P>0.05$), 6 hour ($P<0.001$) and 9 hour ($P<0.001$) as compared to the controls. On the other hand in child class C the Caffeine concentration was remaining same as in their controls.

Conclusion: Caffeine clearance could provide a practical assessment of hepatic function in cirrhotic patients. Our data emphasize the value of the Child-Turcotte or Child-Pugh classification in assessing the severity of liver cirrhosis in a simpler and less time-consuming way than using quantitative liver function tests.

Key Words: Cirrhosis, Caffeine clearance, Child's Pugh classification.

INTRODUCTION

Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules , leading to loss of liver function. It is most commonly caused by alcoholism, hepatitis B and C, and fatty liver disease. However some cases are idiopathic[1].

The prevalence of cirrhosis in patients with chronic HCV increases with increasing duration of infection. In Asian patients infected at birth, infection for over 60 years causes cirrhosis in 71% of infected individuals[2].

Ascites is the most common complication of cirrhosis, and is associated with a poor quality of life, increased risk of infection, and a poor long-term outcome[3]. Other potentially life-threatening complications are hepatic encephalopathy and bleeding from esophageal varices[4].

Assessment of live function is an important work-up for patients with liver cirrhosis. The gold standard for diagnosis of cirrhosis is a liver biopsy. A biopsy is not necessary if the clinical, laboratory suggests cirrhosis. Furthermore, cirrhosis itself predisposes for complications due to liver biopsy[5]. Quantitative tests of liver function (QTLF) measure the elimination of substances that have been either metabolized or excreted by the liver. Elimination of QTLF substances correlates with the amount of blood flow to the liver and with hepatic metabolic capacity. Caffeine is now widely used to assess genetic, environmental and race/breed differences for some enzymes and the hepatic metabolic capacity (total activity of enzymes metabolizing CF) because of its pharmacokinetics and almost complete biotransformation by some CYP 450 enzymes in liver. It is used to analyze microsomal metabolic liver function[6,7].

Serum Caffeine clearance determined at two points of blood concentration is a useful method to evaluate the severity of liver disease and predict short-term survival of cirrhotic patients. It offers another choice for the quantitative measurement of liver functional reservoir[8,9].

Caffeine (CF) concentrations correlated well with the score indicating the sufficiency of the organ according to Child- Turcotte classification score. Caffeine metabolizes solely in the liver. The disappearance of Caffeine was significantly decreased in cirrhotics[10].

The apparent Caffeine clearance in cirrhosis decreased with increasing Child-Turcotte classification score: Child's class A patients differed significantly from Child's class B or Child's class C patients, whereas the difference between Child's class B and C patients did not reach statistical significance (Wilcoxon's rank test). In addition there was a strong correlation between the Child-Pugh classification score and apparent Caffeine clearance[11]. On the other hand a good correlation between impairment of Caffeine elimination and assessment of severity of liver disease[10].

Fasting plasma Caffeine concentrations, however, were significantly higher in cirrhotics than in controls[12]. Recently it is found that there is a significant correlation between CF clearance and the ratio of Caffeine with its metabolites like plasma paraxanthine (PX), theobromine (TB), and theophylline (TP)/CF ratio at 7 hr after creatinine clearance administration[13]. However, a careful dietary history showed no significant difference in Caffeine consumption among cirrhotics vs. control patients[12].

Quantitative assessment of live function is an important work-up for patients with liver cirrhosis. The aim of the present study was to clarify the role of Caffeine clearance test in the quantitative measurement of metabolizing capacity of the liver.

MATERIALS AND METHODS

Forty patients with liver cirrhosis with age range 40-55 years and 20 aged matched normal healthy volunteers were enrolled in this study. Patients were taken from the medical ward of Services Hospital Lahore. Duration of study is 4-5 months. Letter of consent was taken and a certificate from Ethical Committee was also obtained. After an overnight fast, the first blood sample was collected at 8 a.m., immediately followed by an oral administration of 200 mg Caffeine. Subsequent samples of venous blood were obtained at 8.30 a.m., 9 a.m., 11 a.m., 2 p.m. and 5 p.m. Blood level was collected before and after an oral dose of Caffeine. The Caffeine clearance was determined by reversed-phase high pressure liquid chromatography using a Phenomenex Gemini C18 column using a wavelength of 273 *n*m. The mobile phase consisted of 30% methanol in 25 mM Sodium acetate buffer, pH 4.0. The flow rate was 1.0 m*l*/min[13].

Statistical Analysis: The data was analyzed by using SPSS-16.0. Qualitative variables were presented with frequency distribution and percentages. Quantitative variables were reported by using mean±S.D. Variables were calculated and compared with normal control subjects using student 't' test. P value <0.001 was considered as highly significant.

RESULTS

Physical examination findings in cases and controls were presented with frequency distribution and percentages. Jaundice presented with highest frequency distribution and percentages. This was followed with ascities, edema, family history of hepatitis/jaundice and anemia. In control family history of hepatitis /jaundice was presented with a frequency distribution of 3 and 17 while percentage was 15 and 85%. Edema was observed with a frequency of 2 and a percentage was 10 (Table 1).

Ultrasonographic findings showed that in most of the patients, liver is enlarged with a frequency distribution of 21 and have a percentage of 52.5%. On the other in remaining number of patients the frequency distribution of normal and enlarged is same (9-10 was frequency distribution and 22.5-25% was percentage). In controls all cases having normal liver size (Table 2).

Table No. 1: Physical examination findings in cases and controls

Physical examination	Freq and percent Cases (40)	Freq and percent of Controls (20)
Edema	21 52.5%	02 10%
Anemia	16 40.0%	01 05%
Jaundice	25 62.5%	00 0.0%
Ascities	23 57.5%	00 0.0%
Family history of hepatitis/jaundice	21 52.5% 19 47.5%	03 15% 17 85.0%

Table No.2: Ultra sonographic findings in cases and controls

Liver size	Cases with freq and percent (40)	Controls with freq and percent (20)
Normal	09 22.5%	20 100.0%
Enlarged	21 52.5%	00 0.0%
Shrunken	10 25.0%	00 0.0%

Caffeine concentration in CHILD class A, Class B and Class C was observed at baseline, 3, 6 and 09 hours. It was observed in child class A the Caffeine concentration was significantly decreased at base line (P<0.001), 3 hours (P<0.05), 6 hour (P<0.001) and 9 hour (P<0.001) as compared to the controls. In child class B the Caffeine concentration was significantly decreased at base line (P<0.001), 3 hours (P>0.05), 6 hour (P<0.001) and 9 hour (P<0.001) as compared to

the controls. On the other hand in child class C the Caffeine concentration was remaining same as compared to their controls (Table 3).

Table No.3: Caffeine concentration in CHILD class A, Class B and Class C at baseline, 3, 6 and 09 hours.

Caffeine concentration (µg/dl)	Child class A (n=13)	Child class B (n=27)	Child class C (n=07)	Control (20)
Baseline	0.2±0.08**	0.30±0.09**	0.81±0.11	0.81±0.11
3 hours	7.4±0.20*	7.71±0.13	7.75±0.10	7.75±0.12
6 hours	6.51±0.23**	6.72±0.16**	7.32±0.19	7.32±0.19
9 hours	3.65±1.47**	6.32±0.75**	7.12±0.05	7.12±0.05

*P<0.05 = Significant difference
**P<0.001 = Highly significant difference

DISCUSSION

Physical examination findings in cases and controls were presented with frequency distribution and percentages. Jaundice presented with highest frequency distribution and percentages (62.5%). Our study is in accord with a study who found jaundice in 64% cases[14]. It is thought that jaundice may be due to complicated chronic liver disease. Ascities was seen in 57.2% cases. A study stated that 48% patients with cirrhosis develop ascites[15].

Ultrasonographic findings showed that in 50% of the patients, liver is enlarged. Normal liver and shrunken liver is observed in 50%. A study also reported structural changes in liver with cirrhosis[16].

Present study observed an inverse relationship between Caffeine clearance and the degree of fibrosis which had been assessed by comparing the Caffeine clearance in controls, Child class A, Child class B and Child class C patients. Cirrhosis was characterized by a statistically significant reduction in apparent Caffeine clearance. The Caffeine clearance was significantly reduced in Child class B patients when compared to Child class A patients. This may show that the Caffeine clearance in cirrhosis was decreased with increasing Child Pugh classification score and it may be used to measure the metabolizing capacity of the liver quantatively. A study reported that poor prognosis was associated significantly with increasing Child-Pugh score[17]. Present study observed that in Child class C there is no difference in Caffeine clearance in fasting, after 3, 6 and 9 hours as compared to control.

A significantly negative relationship between the serum Caffeine clearance and the Child-Pugh's score was also demonstrated by a group of workers. Their study observed that during the mean six-month period of follow-up, the mortality rate was significantly higher in those patients with Caffeine clearance less than 0.5 ml/min/kg than in those with clearance more than 0.5 ml/min/kg[8,18]. A study also observed that the Caffeine blood concentrations in patients were significantly higher than those in healthy controls. Caffeine concentrations correlated well with the score indicating the sufficiency of the organ according to Child. Their study reported that differences in comparison with controls were the more evident the greater was the degree of liver damage[19]. A group of workers observed that cirrhosis had no effect on the apparent volume of distribution of Caffeine but clearance of Caffeine was substantially reduced in these patients. Production of the three metabolites of CA, but mainly PX, was reduced in patients with cirrhosis[20].

Present study observed the base line Caffeine concentration in Class A patients (0.2 µg/ml), in class B patients (0.3 µg/ml) and in class C patients was 0.81 µg/ml. In case of Child class C there is no difference in Caffeine clearance as compared to controls. Our study is in contrast to a study who observed that fasting plasma Caffeine concentrations in cirrhotics varied significantly with Child's criteria, namely Child's A patients (2.06 µg); Child's B patients (6.92 µg/ml), and Child's C patients (17.70 µg/ml)[12].

Our study is agreed with a study who observed that the semi-quantitative Child-Pugh score is frequently used to assess the severity of liver function impairment especially in Child class C patients, but only offers the clinician rough guidance for dosage adjustment because it lacks the sensitivity to quantitate the specific ability of the liver to metabolize individual compound or drugs[21].

CONCLUSION

Caffeine clearance could provide a practical assessment of hepatic function in cirrhotic patients. Our data emphasize the value of the Child-Turcotte or Child-Pugh classification in assessing the severity of liver cirrhosis in a simpler and less time-consuming way than using quantitative liver function tests.

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