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Role Of Cafts As An Assessment Tool During Acute Withdrawal Syndrome In Chronic Alcoholic Patients: Correlation With Severity Of Disease By Estimation Of Liver Enzymes

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Abstract

Background: Alcoholism reduces person's life expectancy by around ten years. The most common cause of death in alcoholics is due to cardiovascular complications. Particularly during withdrawal from alcohol dependence, the cardiovascular symptoms can be so fatal if it is not properly managed. Alcohol dependence occurs due to the increase in stimulation of the $GABA_A$ receptor, promoting CNS depression. These receptors during chronic alcoholic dependence get sometimes desensitized and reduced in number resulting in tolerance and physical dependence.

Aim Of The Study: To evaluate the various autonomic changes during acute withdrawal syndrome in chronic alcoholic patients & to correlate HRV parameters with their liver function parameters to assess the severity of autonomic dysfunction

Methods: this Cross-sectional analytical study was conducted over 1 year from 2021 at Aarupadai Veedu Medical College & Hospital, Pondicherry and the patients with chronic alcoholism of age 35- 60 years currently in active alcohol dependence by fulfilling ICD-10 criteria. 80 Patients with Chronic alcoholism who were involved in conventional medical management were recruited after obtaining informed consent from Deaddiction center, AVMC, Puducherry and Narmatha Matha deaddiction center, Ariyankuppam, Pondicherry. Along with Parameters such as Pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP), Cardiovascular Autonomic Function Tests (CAFTs) was done by the MP45 biopic two-channel data acquisition software system by which RMSSD, NN50, PNN50, LF, HF, LF: HF, and 30:15 ratio (Time domain & frequency domain indices) LFT parameters were also evaluated.

Results: The mean age of the alcohol dependence group was found to be 43 ± 11.5 and the distribution of subjects in the study group was uniform. The mean SBP in the study group was 133.2± 12.9 and the mean DBP in the study group was 86.3 ± 9.3. Concerning the SBP and DBP, the subjects in the study group showed higher Blood pressure variability due to their derangement in autonomic dysfunction. The mean heart rate was 93 ± 11.6 and it was increased during acute withdrawal syndrome phase in chronic alcoholic patients. the time-domain indices have been altered in alcohol-dependent subjects during acute withdrawal syndrome showing sympathetic predominance. The mean value of GGT was significantly increased in predominant patients with mean of 255.9 ± 249.3 showing gross liver dysfunction with significant negative correlation with LF and LF/HF ratio. Also, the parameters like SGOT, and SGPT were increased in chronic alcoholic patients with significant

negative correlation with LF/HF ratio. RMSSD, a measure of HRV which reflects the integrity of autonomic control has significant negative correlation with duration of alcoholism.

Conclusion: HRV and Liver function tests can be used in alcohol-dependent subjects for follow-up and to determine the prognosis of treatment during Acute withdrawal phase. Bio-feedback of their heart rate variability and liver function tests can help in early intervention to quit alcohol dependance.

Keywords: HRV, liver dysfunction, Autonomic function

Introduction

The World Health Organization (WHO) estimates that as of 2010 there were 208 million people with alcoholism worldwide. Its occurrence is more common among males and young adults. Alcoholism directly resulted in 139,000 deaths in 2013, up from 1,12,000 deaths in 1990. [1]A total of 3.3 million deaths (5.9% of all deaths) are believed to be due to alcohol. Alcoholism reduces a person's life expectancy by around ten years. [2] The most common cause of death in alcoholics is due to cardiovascular complications. Particularly during withdrawal from alcohol dependence, the cardiovascular symptoms can be so fatal if it is not properly managed. Alcohol dependence occurs due to the increase in stimulation of the $GABA_A$ receptor, promoting CNS depression. These receptors during chronic alcoholic dependence get sometimes desensitized and reduced in number, resulting in tolerance and physical dependence. They experience more negative emotional stress during early withdrawal characterized by depressed mood, elevated anxiety, life-threatening seizures, delirium tremens, hallucinations, and autonomic hyperactivity. [3] The acute withdrawal phase can be defined as lasting between one to three weeks after deaddiction. And about a quarter of alcoholics, experience anxiety and depression for nearly 2 years in post addiction period. Alcohol has a deleterious effect on a multitude of systems within the body, adversely influencing neural function, cardiovascular physiology, metabolism, thermoregulation, and skeletal muscle myopathy.[4] The sympathetic activity which is responsible for “the fight or flight response” increases heart rate and blood pressure. Parasympathetic activity which is conveyed through the vagus nerve is responsible for relaxation and restoration of heart rate, in which heart rate and blood pressure decrease. The body works most effectively when there is high parasympathetic activity.[5] cardiovascular autonomic function testing provides an early screening and therapeutic tool in the assessment of Acute withdrawal symptoms. And this present study is designed to know the efficacy of CAFTs as an assessment tool in the acute withdrawal phase, which is correlated with various factors like duration and severity of the alcohol dependence and with the signs of Liver damage which is lacking in the literature.[6] Thus HRV and Liver function tests can be combined and used as a prognostic tool in these subjects and early intervention of them with alcohol abstinence, nutrition supplementation can prevent alcoholic cardiomyopathy and alcoholic liver disease.[7]

Methods: This Cross-sectional analytical study was conducted over 1 year from 2021 at Aarupadai Veedu Medical College & Hospital, Pondicherry and the patients with chronic alcoholism of age 35- 60 years currently in active alcohol dependence by fulfilling ICD-10 criteria. 80 Patients with Chronic alcoholism who were involved in conventional medical management was recruited after obtaining informed consent from Deaddiction center, AVMC, Puducherry and Narmatha Matha deaddiction center, Ariyankuppam, Pondicherry. Along with Parameters such as Pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP), Cardiovascular Autonomic Function Tests (CAFTs) was done by the MP45 biopic two-channel data acquisition software system and the parameters like RMSSD, NN50, PNN50, LF, HF, LF: HF, and 30:15 ratio (Time domain & frequency domain indices) LFT parameters were also evaluated. ECG was recorded for 10 minutes for short-term analysis. The procedure was done with the subjects made to lie in a supine position on a couch, awake with eyes closed. The ECG recordings with normal sinus rhythm for 5 minutes were taken for analyzing the heart rate

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variability, excluding the artifacts. The Task Force European Society of Cardiology guidelines were followed while recording and analyzing HRV data. Using time domain and frequency domain indices, the heart rate variability was analyzed. To calculate the Time domain indices, each QRS complex is identified and the normal to normal (N – N) intervals (the intervals between the adjacent QRS complex) is determined. Liver function tests to be measured were GGT, ALT, AST, ALP, total protein, albumin, globulin, total bilirubin, and direct and indirect bilirubin. The subject was made to sit comfortably. A tourniquet was applied to the arm above the cubital fossa. Following aseptic precautions, 2 ml of blood was withdrawn from the antecubital vein of the forearm of the subject. The blood sample was then transferred to EDTA coated vacutainers and was appropriately labeled. The needles, syringes, and cotton swabs were discarded appropriately. The blood samples collected in the EDTA coated vacutainer was placed in a centrifuge machine and centrifuged for 15 minutes at 3000 revolutions per minute. The liver function test values of chronic alcoholic patients were obtained and tabulated for correlation analysis with HRV parameters

Statistical Analysis:

The results obtained were entered in excel sheet and analyzed by SPSS 2.0 and expressed as Mean and Standard deviation (SD) for normal data distribution (Mean ± SD). Categorical variables were expressed in percentages. Continuous values were expressed in mean ±SD. Correlation regression analysis was done used

P value of less than 0.05 is considered as significant.

TABLE 1 :Anthropometric parameters &vital parameters expressed in mean ± SD in chronic alcoholic patients

	Min	Max	Mean (SD)	Median
Age (years)	19	71	43.0 (11.5)	43.5
Height (in cm)	144.0	179.0	162.0 (7.7)	160.5
Weight (in kg)	45.0	90.0	66.3 (12.0)	65.0
BMI (in kg/m^2)	19.0	34.7	25.2 (4.2)	24.4
Waist circumference (cm)	70.0	106.0	84.6 (7.1)	85.0
Pulse Rate (beats/min)	70	122	93 (11.6)	91
Respiratory Rate (breaths/min)	14	18	16.2 (1.2)	16
Systolic BP (mmHg)	100	160	133.2 (12.9)	135
Diastolic BP (mmHg)	70	100	86.3 (9.3)	90

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Table:1 The mean age of the alcohol dependence group was 43 ± 11.5. Regarding age, the distribution of subjects in the study group was uniform. The mean SBP in the study group was 133.2± 12.9 and the mean DBP in the study group was 86.3 ± 9.3. Concerning the SBP and DBP, the subjects in the study group showed higher Blood pressure variability. The mean heart rate was 93 ± 11.6. The mean BMI among the study group was found to be less (25.2 ± 5.2) and the mean Waist circumference 84.6 ± 7.1

TABLE 2: Liver function parameters

	Min	Max	Mean (SD)	Median
Total Bilirubin	0.40	6.50	1.46 (1.02)	1.35
Direct Bilirubin	0.10	5.0	0.88 (0.83)	0.80
Indirect Bilirubin	0.20	2.0	0.85 (0.44)	0.85
SGOT	12.0	426.0	153.2 (117.5)	116.0
SGPT	11.0	595.0	129.3 (115.9)	96.0
GGT	38.0	1210.0	255.9 (89.3)	118.0
ALP	6.90	403.0	151.5 (78.7)	134.0
Total Protein	3.8	8.4	6.9 (0.8)	6.8

Table 3: time-domain indices in chronic alcoholic patients during acute withdrawal syndrome

	Min	Max	Mean (SD)	Median
RMSSD	11.7	125.2	42.7 (25.5)	35.2
NN50	1.0	222.0	67.0 (56.1)	49.5
PNN50	0.20	77.4	26.7 (23.6)	16.9
LF	7.8	51.1	24.8 (11.0)	23.7
HF	9.0	74.9	38.8 (20.5)	38.6
LF: HF	0.174	4.40	1.01 (0.64)	1.07

Table 3: Heart rate variability indices include Time Domain parameters and Frequency domain parameters. The time-domain parameters which includes mean RMSSD, NN50, pNN50

Table 4: Correlation analysis of LFT & HRV parameters

		RMSSD	**NN50**	**PNN50**	**LF**	**HF**	**LFHF**
SGOT	Correlation Coefficient	.166	-.063	-.116	-.278	.265	-.375*
	p-value	.305	.699	.476	.082	.098	**0.017**
SGPT	Correlation Coefficient	.124	-.048	-.061	-.175	.233	-.277
	p-value	.447	.771	.707	.279	.149	.083
GGT	Correlation Coefficient	.001	-.259	-.159	-.346*	.119	-.369*
	p-value	.997	.106	.327	**0.029**	.463	**0.019**

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ALP	Correlation Coefficient	.239	.093	-.002	.011	.080	-.023
	p-value	.137	.570	.988	.944	.624	.890
Spearman's Correlation Coefficient used; p-value <0.05 is significant;							

Table 5: Correlation analysis between duration of alcoholism & HRV parameters

		CIWA	SADQ	RMSSD	NN50	PNN50	LF	HF	LFHF
DURN	Correlation Coefficient	.150	.143	.400*	-.292	-.272	-.193	-.195	.003
	p-value	.354	.377	**.011**	.067	.090	.233	.227	.987
CIWA	Correlation Coefficient		.128	.095	.075	-.011	-.062	-.014	-.066
	p-value		.432	.561	.645	.946	.704	.930	.687
SADQ	Correlation Coefficient			.125	.053	-.008	-.136	.265	-.284
	p-value			.442	.747	.959	.403	.099	.076
Spearman's Correlation Coefficient used; p-value <0.05 is significant;									

Discussion

Alcohol dependence (AD) is resistant to treatment and many patients relapse within the first year of the following care. There is a need for better understanding the specific factors that predict and moderate treatment response to help in the formulation of improved treatments for AD. One promising individual difference factor that is thought to influence AD treatment efficacy is the ability to regulate affect, that is, an individual's ability to understand or accept his or her emotional experience, engage in strategies to manage uncomfortable emotions adaptively, and respond appropriately to negative mood. Indices of heart rate variability (HRV), an electrocardiogram (ECG) derived measures of neurocardiac signaling, were used to operationalize modulation of psychophysiological arousal. Potential differences in the relationship of HRV to anxiety and depression in participants with symptoms of cluster-B personality disorders (PDs) were also explored.[8] There exist a need to analysis the emotional component involved during Acute Withdrawal phase in chronic alcoholic patients which can produce influence in the autonomic function of the individual. And thereby understanding their Autonomic influences, it remains a mainstay of treatment intervention. The major cause of death in chronic alcoholism patients is Cardiovascular morbidity. And the pathophysiology behind this concept has to be addressed in the early phase and well appraised to them patients. HRV is a sensitive and specific tool to assess the autonomic function and used worldwide as a specific marker. In our present study, the mean age of the alcohol dependence group was found to be 43 ± 11.5 and the distribution of subjects in the study group was uniform. Height in centimeters and weight in kilograms were also measured. Body mass variability. The mean heart rate was 93 ± 11.6 and the resting heart rate was found to be higher in the study group as described in many of the studies. An increase in heart rate was observed in the study group due to an increase in the sympathetic activity secondary to vasodilation or increased calcium entering into cardiac myocytes. [10] [11] In our study the mean of NN50 and pNN50 values were significantly reduced in the chronic alcoholic patients considering the fact that they were more prone index (BMI) was calculated using the Quetelet formula. The mean BMI among the study group was found to be less (25.2 ± 5.2) and the mean Waist circumference 84.6 ± 7.1. The mean SBP in the study group was 133.2± 12.9 and the mean DBP in the

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study group was 86.3 ± 9.3. Concerning the SBP and DBP, the subjects in the study group showed higher Blood pressure to have cardiovascular risk.

The mean RMSSD was shown to increase in the acute withdrawal phase which indicates reduced parasympathetic activity in the heart or sympathetic dominance. [12] This depicted specific markers of vagal activity like RMSSD and PNN50 values well documents the autonomic blunting or dysfunction phase in patients with chronic alcoholism. These values were reduced showing a gross reduction in vagal activity, reflecting vagal neuropathy or reduced parasympathetic activity which happens during acute withdrawal phase. [13] It can be explained as an early marker for deranged cardiac autonomic function and plan for an early intervention. Malave HA et al did an extensive study on parasympathetic dysfunction affecting the vagus nerve in patients with chronic alcoholism, which showed depressed reflex heart rate responses due to parasympathetic neuropathy. Our study supports the same indicating that alcoholic autonomic neuropathy primarily affects the parasympathetic system than the sympathetic system. The frequency domain indices analyzed are LF, HF, and LF/HF ratio. The mean values of LF and HF in ms^2 were 24.8 ± 11.0 and 38.8 ± 20.5 respectively. The mean value of HF power 38.8 ± 20.5 has got decreased during their alcohol dependance phase showing altered sympathovagal balance [14]. This predominant vagal neuropathy with decreased parasympathetic activity [15] explained the following mechanism: Cytokines released from alcohol metabolism in the liver cause autonomic dysfunction and blunting of β-adrenergic signaling contributing to reduced HRV. Cytokine-induced neural modulation affects the brain cortex and the subcortical regions like the medullary centers. The central cardiovascular medullary center is disordered by cytokines, resulting in the uncoupling of the cardiac pacemaker cells from their brain stem regulators. This is implicated in the reduced heart rate variability.[16] Chronic alcohol intake causes nutritional deficiency. Chronic thiamine deficiency in alcoholics can also lead to nerve cells degeneration, reactive gliosis, and atrophy of the cerebellum and peripheral nerves including autonomic nerves. Therefore, deficiency of nutritional factors was also responsible for vagal neuropathy in chronic alcoholics has been well established in many of the literature [17] Chronic alcoholism causes a direct dose-dependent toxicity to the autonomic and peripheral nervous systems. The mean value of GGT was significantly increased in the alcohol dependent patients with mean value of 256±.89.3. GGT remains as a sensitive test to evaluate the signs of liver damage

High levels of GGT in the blood could indicate that there exists a leakage of enzymes out of the liver cells and into the blood. This may suggest a possible damage to the liver or bile ducts. GGT levels rise according to the amount of liver damage a patient has. High GGT levels could indicate liver damage, though it does not diagnose the specific cause. A person often needs follow-up tests to determine the reasons for the elevated GGT levels. Here in our study this level of GGT showed significant negative correlation with LF /HF ratio which clearly tells that there exists an autonomic dysfunction along with the signs of liver damage. And the mean value of the parameters SGOT & SGPT were significantly raised. [18],[19]. Increased liver enzymes in alcoholics indicate hepatic dysfunction and had a positive correlation with RMSSD. Elevation of liver enzymes like GGT, SGOT & SGPT, the essential tool for abnormal liver function. All the above-mentioned liver enzymes showed significant negative correlation with LF/HF ratio depicting altered Sympathovagal balance. Chronic alcoholism leads to serious hepatic cell injury which cannot be reversed with the stoppage of alcohol. This leads to the release of liver enzymes stored within the hepatocytes into the circulation leading to elevated liver enzymes in the blood. [20] Gamma-glutamyl transferase, a sensitive marker of alcohol intake, liver dysfunction, and oxidative stress. It is a biliary canalicular enzyme induced by alcohol, and their serum levels rises in response to hepatocellular damage. [21] Thus high levels of GGT in alcoholics indicate that they are at risk of suffering irreversible liver damage. In alcohol-dependent subjects, SGOT and SGPT enzymes which are normally present in higher concentrations in hepatocytes leak into the circulation when hepatocytes or their cell membranes get significantly damaged.[22] By assessing the liver enzymes and correlating with HRV parameters aids us in describing the autonomic functional status in chronic alcoholic patients because the major cause of serious outcomes in these patients can be underlying cardiovascular derangement. And assessing the

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cardiovascular autonomic function in such patients during their withdrawal phase undoubtedly tells us their strength of Alcohol dependance. This was very evident from our study by correlating the HRV parameters with the duration of alcohol dependance. It was clearly evident that exist a significant positive correlation with RMSSD. The RMSSD reflects the beat-to-beat variance in HR and is the primary time-domain measure used to estimate the vagally mediated changes reflected in HRV (23) and this warrants an early intervention in these chronic alcoholic patients during their acute withdrawal phase. This early intervention can be helpful in assessment of outcome of deaddiction in a very early phase and plan for other modalities of treatment in chronic alcoholism [24,25].

Conclusion

The resting heart rate variability showed increase in the time domain parameters (RMSSD, NN50, pNN50) indicating reduced parasympathetic activity. In the frequency domain measures, the mean value of HF power has got decreased during their alcohol dependance phase showing altered sympathovagal balance. LF/HF ratio was altered indicating Sympatho-vagal imbalance. Therefore, from the results of our study on Heart rate variability, we conclude there exist a Sympatho-vagal imbalance having predominant vagal neuropathy with decreased parasympathetic activity during acute withdrawal phase in alcohol-dependent individuals. Elevated liver function enzymes and increased GGT, SGOT levels were seen in the alcohol-dependent subjects indicating the toxic effect of alcohol on the liver and showed significant correlation with RMSSD and LF/HF ratio. Moreover, the duration of alcohol dependence showed positive correlation with RMSSD depicting its role in cardiovascular derangement. If intervention can be initiated at the earliest, progression of liver cell damage to cirrhosis can be prevented. Thus, a non-invasive tool like HRV can be used in alcohol-dependent subjects for follow-up, to assess the severity of the disease and to determine the prognosis. Thus, HRV and Liver function tests can be combined and used as a prognostic tool in these subjects for an early intervention to bring out alcohol abstinence and administration of other modalities of treatment protocols available like Yoga, meditation and nutrition supplementation for obtaining better prognosis.

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