EFFECT OF CHRONIC HASHISH CONSUMPTION ON LIVER FUNCTION AND COAGULATION PROFILE IN HASHISH USERS

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ABSTRACT

Objective: To study the effect of hashish consumption on liver function and coagulation parameters.

Methodology: Chronic hashish consumers (n=62) and healthy controls (n=43) were studied. Serum bilirubin, Liver enzymes alanine transaminase and alkaline phosphatase were studied to evaluate hepatic malfunctioning using manual colorimetric method. The coagulation parameters prothrombin time and activated partial thromboplastin time were studied to evaluate the risks of bleeding disorders using manual-tilt method.

Results: An increase in the blood levels of total bilirubin (P= 0.014), alanine transaminase (P= 0.024) and alkaline phosphatase (P= 0.025) was observed in chronic hashish consumers as compared to the non-hashish using group. A significant prolongation in prothrombin time (P= 0.026) and activated partial thromboplastin time (P= 0.029) was found in chronic hashish consumers as compared to the control group.

Conclusion: An increase in the levels of liver enzymes and coagulation parameters were observed in hashish users as compared to the control group which indicates that hashish consumption affect the liver functions.

Key Words: Hashish, Liver enzymes, Coagulation

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INTRODUCTION

Liver plays a very important role in homeostasis of body by different mechanisms among which one is coagulation. It functions as the production site of almost all clotting factors and their inhibitors[1]. Any damage to liver can develop an increased risk of localized bleeding up to life-threatening hemorrhage or thrombosis by developing multiple coagulation abnormalities resulting from an imbalance between coagulation and fibrinolysis[2]. Different etiologies of chronic liver damage may include viral infections and alcoholic and non-alcoholic fatty liver disease etc.[3]. Clinicians and researchers have shown interest in evaluating liver functioning by determining the blood levels of some coagulation factors. One of the study reported that about 85% of patients suffering from liver malfunctioning have at least one or more coagulation related abnormalities[4]. The coagulation abnormalities in liver injuries are usually measured by evaluating prothrombin time (PT) and the activated partial thromboplastin time (APTT). Increased PT and APTT are related to the severity of hepatic failure leading to bleeding risks and mortality[5-7].

In Pakistan, approximately 6.7 million people (6% of the population) use controlled substances in which cannabis (hashish) is commonly used drug with a prevalence of 3.6%. Khyber Pakhtunkhwa is the province of Pakistan with overall highest prevalence of any form of drug abuse with 10.9% of the population using illicit substances[8]. Presently, cannabis is considered to be the most common forbidden substance known that is followed by cocaine, amphetamines and opioids with diverse occurrence in different countries[9]. The consumption of cannabis as hashish in the body metabolizes into two major metabolites: cannabidiol (CBD) and tetrahydrocannabinol (THC), that binds to cannabinoid receptors, specifically to CB1 receptor, which further links to the progression of fibrosis, cirrhosis and other hepatic diseases[10].

Studies have been published regarding the effect of cigarette smoking, alcohol intake and other controlled drugs on various biochemical parameters of body including lipid profile, coagulation parameters and hematological indices[11-13] that ultimately play degenerative role in disorders of brain, liver, heart, lungs and blood[14-19]. However studies regarding the potential role

of hashish consumption on the blood coagulation parameters and liver function parameters are very limited. The current study aims to evaluate the potential role of hashish consumption on liver, by measuring liver enzymes that cause liver parenchymal damage and by measuring coagulation parameters leading to bleeding disorders.

METHODOLOGY

A total of 105 adult subjects were included with an age greater than 20 years (range 20-60 years). The subjects were divided into two groups as Hashish users (n=62) and control group (n=43). Study subjects for this study were selected from Peshawar, Pakistan. All the subjects were enrolled in the current study as per criteria; more than 20 years old men with no past history of medicine intake for at least two weeks, no major clinical illness, minimum duration of substance use of 5 years, and willingness to give consent. Exclusion criteria included age less than 20 years, multiple drug abuse, hematological disorders, malignancies and hypertension. The subjects with hashish use in this study were individuals who consumed hashish (>3g per day) via direct smoking (local name Chitta) using resin pipes and water filters. Duration of hashish consumption among the subjects ranged from 5-30 years. Control group included participants with non-users of the same age and area.

The study protocols was designed according to Helsinki Declaration 1964 and was approved by the Ethical committee of Department of Pharmacy, University of Swabi, Pakistan. Written consent on informed consent form was obtained from all the study participants.

Fasting blood samples from both the groups were collected in disposable syringe (5ml) using standard aseptic technique and was divided into two parts; one part in EDTA tube and the other in Gel tube (without anticoagulant) for serum separation. All selected subjects were investigated for PT, APTT, serum bilirubin, ALT and ALP. Samples were prepared at the Department of Pharmacy, University of Peshawar and the investigations were performed at Al-Shifa Laboratories & diagnostic center, Peshawar. PT and APTT were performed on manual-tilt method using hemostat reagent kits and Liver enzymes were determined using manual colorimetric method.

Data were analysed using the GraphPad Prism biostatistical software package (version 5.01, GraphPad Software, Inc., CA, USA). The coagulation parameters and liver function parameters between the study groups were compared using unpaired two tailed student "t"-test. P value <0.05 was considered as statistically significant.

RESULTS

One hundred and five, 62 hashish users and 43 age and gender matched controls, aged 20-60 years (mean age 35.61 ±7.23 years) were enrolled in this study (See Table 1). The duration of hashish consumption by hashish users was 20.2 ±6.63 years while the quantity of hashish consumption by this group was 4.3 ±2.28 grams per day.

In the study group, the mean values of PT and APPT were 16.2 ±1.4 sec (P= 0.026) and 34.4 ±1.78 sec (P= 0.029) respectively. The mean values of all the three liver function parameters were found to be higher in hashish consumers as compared to the control group with values of 0.75 ±0.16 mg/dl, 41.4 ±26.9 iu/l and 239.4 ±39.39 u/l respectively (Table 2).

The Pearson correlation between coagulation parameters and the duration of hashish addiction revealed no significant result.

Table 1: Characteristics of particpants

Parameter	Control Group (n=42)	Hashish Users (n=63)	P Value
	Mean ± SD		
Age (years)	35.99 ± 1.39	35.23 ± 6.38	0.601
Weight (kg)	72.86 ± 6.08	62.43 ± 12.98	0.132
Body Mass Index (kg/m2)	21.82 ± 3.63	21.69 ± 4.73	0.582
Fasting Blood Sugar (mg/dl)	90.33 ± 8.82	91.35 ± 9.46	0.603
Duration of Addiction (years)	N/A	20.2 ± 6.63	--
Quantity of Hashish Use (grams/day)	N/A	4.3 ± 2.28	--

Table 2: Blood coagulation and liver function parameters in study groups

Parameters	Control Group	Hashish Users	P Value
	Mean ± SD		
Coagulation Parameters			
Platelets Count (×10^3/µl)	225.2 ± 30.4	245.33 ± 68.13	0.324
PT (sec)	14.36 ± 0.37	16.2 ± 1.4	0.026*
APTT (sec)	31.96 ± 0.62	34.4 ± 1.78	0.029*
Liver Function Parameters			
Total Bilirubin (mg/dl)	0.55 ± 0.24	0.75 ± 0.16	0.014*
ALT (iu/l)	20.1 ± 5.8	41.4 ± 26.9	0.024*
ALP (u/l)	173.4 ± 44.4	239.4 ± 39.39	0.025*

* Significant

DISCUSSION

The medical complications caused by substance use such as alcohol, opiates and cocaine have been reported in various case reports and case series. However it has been suggested that detail studies are required to precisely report the actual dose and mechanism of the drug induced complication[20]. Knowledge regarding the relationship between liver pathophysiology and the use of hashish is still scarce. The report given by Indian hemp commission in the 19th century has not discovered any effect on hepatic function among chronic hashish consumers[21]. However later on histopathological changes, alterations in liver enzymes and inflammations have been reported by various studies[13,21,22]. The liver enzymes Alanine transaminase (ALT) and Alkaline phosphatase (ALP) have been considered as vital indicators of hepatocellular injuries resulting from substance abuse. Elevation in the blood levels of these enzymes in hashish users have been previously reported in case of alcoholism, opium addiction and heroin addiction[13, 23,24].

Borini et al[21] in their study reported that hashish smoking on its own or in association with other drugs of abuse has been associated with elevated levels of ALT, aspartate aminotransferase, and ALP along with hepatomegaly and splenomegaly. Similarly, one of other studies reported in humans have observed an increase in ALT and gamma glutamyltransferase activities, along with an increase in the serum level of Bile acids and bilirubin pertaining to chromic hashish smokers with no history of liver disease[25]. This alteration in the enzyme levels may be due to direct role of tetrahydrocannabinol (THC) on the liver or this may be due to indirect role by way of oxidative stress[26]. Oxidative Stress (OS) is physiological disturbance in the balance between the generation of reactive species (ROS/RNS) and the ability of body to scavenge them or can be explained as imbalance between the pro-oxidants and anti-oxidants in the favor of former due to various factors such as aging, toxicity, drug action, inflammation and/or addiction[27]. Oxidative stress has been reflected as one of the major pathological mechanism that contributes to initiate and progress liver injury[28].

Animal studies showed anticoagulant effect of cannabis when administered to rat models. The active components of cannabis, tetrahydrocannabinol and cannabinoids, showed inhibition of thrombin induced clot formation which indicates that hashish is involved in delaying clotting times[29].

Levendal et al. in their study on diabetic rats reported three fold elongations in the blood clotting time after the treatment of animals with Cannabis extract[30]. These results are in accordance with the results reported by us. Similarly, Coetzee C et al[29] in their study on obese rat model reported considerable inhibition of thrombin-induced clot formation in the in-vitro model by administering cannabis abstract. Same was reported in in-vivo model where 50% of clotting times were found to be increased by two times as compared to their control groups. Hence, it can be stated that acute or chronic liver injury may result in decreased production of clotting proteins which may be considered as a reflection of impaired protein synthesis (protein peroxidation) due to oxidative stress condition. This is due to the direct effect of these hashish metabolites on liver by interfering in the physiological pathways of enzymes production or that may be due to the generation of reactive species (reactive oxygen/nitrogen species) which is responsible to directly damage the liver[7].

LIMITATIONS

As the liver is the major organ involved in metabolism of many products, the study may have been limited by some hepatic confounders. Further studies, in-detail, are required to find out the exact mechanisms involved in hashish-induced derangement in coagulation parameters. Furthermore, the female population was not accessed due to cultural and religious limitations.

CONCLUSION

An increase in liver function enzymes and clotting time was observed in hashish addicts as compared to the control group.

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CONTRIBUTORS

AU conceived the idea, planned the study, and drafted the manuscript. AK and ZI supervised the study and provided analytical facilities. IK, LA and WAK helped acquisition of data, did statistical analysis and revised the manuscript critically. MS and SJ helped in sample collection, storage and analysis. MA helped in sample analysis and manuscript writing. All authors contributed significantly to the submitted manuscript.