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RESEARCH ARTICLE **OPEN ACCESS**

Liver Enzyme Analysis in HCV-Infected Patients with Chronic Use of Smoked Opium Derivatives vs. Oral Methadone Consumption

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Abstract:

Background: Hepatitis C is a global issue, causing acute and chronic hepatitis with high mortality. Drug abusers are at the highest risk.

Objectives: This study compares liver enzyme levels in HCV patients using smoked opium derivatives versus oral methadone to assess prognosis and treatment response.Materials and Methods: This descriptive-analytic, retrospective study included 100 participants from a sample of 350, selected based on inclusion criteria. Data were collected via a researcher-designed checklist and analyzed using STATA14 with descriptive and inferential statistics. Covariance analysis was used to control for confounders like time and age.

Results: The mean levels of liver enzymes (ALT and AST) in patients with chronic HCV who consumed methadone orally were 77.25 (SD=8.26) and 78.325 (SD=7.91), respectively. The mean levels of ALT and AST in patients with chronic HCV who smoked heroin were 50.71 (SD=4.88) and 53 (SD=4.69), respectively. The effect of two confounding variables, age, and duration of drug use, on the level of liver enzymes was controlled using covariance analysis. The level of significance of the model was 0.007, which was less than 0.05, indicating that the level of AST and ALT in patients with chronic HCV who consumed methadone orally and smoked heroin was different.

Conclusion: HCV patients using oral methadone show higher ALT and AST levels and greater liver damage than heroin smokers. Alternative treatments to methadone are recommended to reduce liver damage and improve outcomes in these patients.

Keywords: Hepatitis, Methadone, Opium smoking, ALT, AST, HCV.

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1. INTRODUCTION

Hepatitis C is a global health issue, leading to significant morbidity and mortality due to cirrhosis and Hepatocellular Carcinoma (HCC) [1]. The Hepatitis C Virus (HCV), a single-stranded RNA virus from the Flaviviridae family, is primarily transmitted through infected blood [2,3]. Drug users, particularly those who inject drugs, represent the highest-risk group for contracting HCV. In developed countries, a significant proportion of new HCV infections occurs among injection drug users, with infection rates of 70-90% in long-term users [4,5]. While the risk of HCV transmission is lower in users of oral or inhaled drugs, it remains an important concern in the broader context of substance abuse [6, 7].

In Iran, the use of drugs has rapidly increased, with the prevalence of addiction tripling over the past few decades, affecting a significant portion of the population [8,9]. This rise in addiction correlates with a higher incidence of diseases such as HCV, cirrhosis, and liver damage. Hepatitis C infection, particularly in drug users, leads to liver enzyme elevation, with ALT and AST serving as key biomarkers for liver dysfunction [10-16]. Previous studies have shown that drug use, including opium and methadone, exacerbates liver damage in HCV patients, contributing to an increase in ALT and AST levels [17,18].

This study aims to compare the liver enzyme levels (ALT and AST) in chronic HCV patients consuming smoked opium derivatives and oral methadone in Lorestan Province. By focusing on the differences in liver enzyme levels between these two groups, this research seeks to contribute to understanding the impact of substance use on liver function in HCV patients and inform prognosis and treatment strategies.

2. MATERIALS AND METHODS

The present study was a descriptive-analytical and retrospective research. After obtaining permission from the Ethics Committee and Research Committee of Lorestan University of Medical Sciences (IR. LUMS. REC. 1400. 156), we visited the archive and documents section of the Hepatitis and Contagious Diseases Center of the Health Deputy of Lorestan Province.

Based on previous studies, about 350 patients with hepatitis C have been identified in Lorestan Province. The definite diagnosis of hepatitis C patients included in the study had to be confirmed by the HCV_RNA_PCR method based on previous documents in the file. According to the predetermined criteria for entering and exiting the study, we selected patients based on the information recorded in their files. Most of the desired information related to the study variables was recorded in the files. However, regarding incomplete files, with prior coordination with the health center, treating physician, and advisor, we contacted the patients via the phone numbers registered in their files. After introduction, ensuring their privacy and explaining the purpose of the research project while reassuring them about the confidentiality of their information, we collected and recorded other relevant information such as the type of drug used, duration of drug use, and method of drug use based on their self-declaration and medical history. Finally, out of 350 patients with HCV, based on the entry and exit criteria, 100 eligible patients were selected. They were divided into two groups: chronic smoked tramadol users (52 individuals) and chronic oral methadone users (48 individuals). Other demographic information, such as age and gender, was collected and recorded after extraction from the files and entered into the Stata14 software for analysis. All tests were performed using Stata 14 software. To determine descriptive results, the central index and dispersion index were calculated depending on the distribution of variables. Then, to compare the mean responses of interest based on the variable tables and study objectives, a t-test wasused.

The inclusion criteria consisted of all patients with definite HCV infection who were chronic users of smoked opium derivatives and oral methadone during the period from 2019 to 2020 in Lorestan province. Patients who had the following conditions were excluded from the study: those who had less than 1 month of drug use, patients who had used methadone and opium intermittently or recreationally for more than one month and without signs of addiction or withdrawal symptoms caused by the use of these drugs, patients who had other conditions such as diabetes, obesity, non-alcoholic fatty liver, alcohol consumption, use of non-drug hepatotoxic drugs, other infectious diseases, co-infection with other types of hepatitis, a medical history of using a non-opium or methadone drug, and an increase in liver enzyme levels. Patients who used opium orally were also excluded.

Using a census method, all patients with HCV who were chronic users of smoked or oral methadone and opium (with at least 1 month of continuous use and, if withdrawn, exhibit withdrawal symptoms) between2019 and 2020 and had their information registered in the repository of hepatitis and behavioral diseases documents of the Health Deputy of Lorestan University of Medical Sciences, with confirmed hepatitis by HCV_RNA_PCR based on previous documents, were included in the study.

2.1. Data Analysis

Data analysis was performed using software to determine descriptive results, central tendency, and dispersion depending on the distribution of variables. Then, to compare the mean responses based on the variables and study objectives, the t-test was used. Additionally, to control for the confounding effects of time and other quantitative variables such as age, Analysis of Covariance (ANCOVA) was used.

3. RESULTS

The sample includes 82% males and 18% females. Among the participants, 48% use methadone, and 52% use opium. Findings cover age, gender, ALT, AST, usage duration, and substance type.

The averages, standard deviations, and ranges of age, duration of use, and liver enzymes (AST, ALT) were calculated for methadone and opium derivative users. Methadone users had an average age of 43.54 years (SD = 10.52, range: 25–75), a usage duration of 3.39 years (SD = 1.51, range: 1–7), AST levels of 78.33 (SD = 54.82, range: 10–239), and ALT levels of 77.25 (SD = 57.27, range: 18–254).

The average age of opium derivative users is 47.27 years (SD: 11.25), ranging from 31 to 76 years. The average usage duration is 7.71 years (SD: 5.99), with a range of 1 to 31 years. The average AST level is 53 (SD: 33.83), ranging from 14 to 228, and the average ALT level is 50.71 (SD: 35.19), ranging from 10 to 236.

The average age of methadone and opium users is 45.48 years (SD: 11.01), ranging from 20 to 76. The average usage duration is 5.64 years (SD: 4.92), with a range of 1 to 32 years. The average AST level is 65.3 (SD: 46.71), ranging from 10 to 239, and the average ALT level is 63.45 (SD: 48.71), ranging from 10 to 254.

The average age of male users is 45.36 years (SD: 10.27), ranging from 25 to 76, with an average use duration of 6.02 years (SD: 5.29), ranging from 1 to 32 years. The avergae male AST level is 68.08 (SD: 49.68), ranging from 10 to 239, and the avergae ALT level is 65.78 (SD: 51.64), ranging from 15 to 254.

The avergae female users is 46 years (SD: 14.25), ranging from 31 to 76, with a use duration of 3.88 years (SD: 1.96), ranging from 2 to 9 years. The average female AST level is 52.61 (SD: 27.15), ranging from 18 to 119, and \ the average ALT level is 52.83 (SD: 31.05), ranging from 10 to 134.

Overall, the average age is 45.48 years (SD: 11.01), ranging from 25 to 76, with an average use duration of 5.64 years (SD: 4.92), ranging from 1 to 32 years. The average AST level is 65.3 (SD: 46.71), ranging from 10 to 239, and the average ALT level is 63.54 (SD: 48.71), ranging from 10 to 254 (Table **1**).

Of 82 male users (82%), 40 (48.8%) use methadone, and 42 (51.2%) use tramadol derivatives. Among 18 female users (18%), 8 (44.4%) use methadone, and 10 (55.6%) use tramadol derivatives. Overall, 48% use methadone, and 52% use tramadol derivatives. The Chi-square test (χ^2 = 0.11, p = 0.739) shows no significant relationship between gender and substance type (Table **1**).

3.1. The Level of the AST Enzyme among Methadone and Tramadol Users

AST levels differ between HCV patients using oral methadone and those smoking heroin derivatives. Methadone users have a mean AST of 78.33 ± 7.91 (95% CI: 62.92–94.32), while heroin derivative smokers have a mean AST of 53 ± 4.69 (95% CI: 43.69–62.30).

A covariance analysis compared AST levels between consumer groups, adjusting for age and drug use history. With a significance level of 0.0055 (<0.05), the AST levels in chronic HCV patients consuming smoked heroin derivatives and oral methadone differ significantly.

Next, these groups compare ALT levels to test whether they differ.

In HCV-infected patients, the mean ALT level is 77.25 (SD: 8.26) for oral methadone users, with a 95% CI of (93.65, 60.84), and 50.71 (SD: 4.88) for smoked heroin derivative users, with a 95% CI of (60.39, 41.03). Covariance analysis, adjusting for age and substance use history, found a significant difference in ALT levels between the groups (p = 0.007) (Table **2**).

Table 1. Analysis of demographic and clinical characteristics of the study participants, classified by gender and type of substance used.

Gender/Group	Age(mean±SD) (Min-Max)	Duration of Use (mean±SD) (Min-Max)	AST(mean±SD) (Min-Max)	ALT(mean±SD) (Min-Max)	Frequency (%)	Cumulative Frequency
male	45.37 ± 10.27 (25-76)	6.02 ± 5.29 (1-32)	68.09 ± 49.68 (10-239)	65.78 ± 51.64 (15-254)	82 (82%)	82
female	46.00 ± 14.26 (31-76)	3.89 ± 1.97 (2-9)	52.61 ± 27.16 (18-119)	52.83 ± 31.06 (10-134)	18 (18%)	100
Methadone Consumer	43.54 ± 10.52 (25-75)	3.40 ± 1.51 (1-7)	78.63 ± 54.82 (10-239)	77.25 ± 57.27 (18-254)	48 (48%)	48
Opium Consumer	47.27 ± 11.26 (31-76)	7.71 ± 5.99 (1-32)	53.00 ± 33.83 (14-228)	50.71 ± 35.19 (10-236)	52 (52%)	100
Total	45.48 ± 11.01 (25-76)	5.64 ± 4.93 (1-32)	65.30 ± 46.71 (10-239)	63.45 ± 48.71 (10-254)	100 (100%)	100

Table 2. ANOVA of AST and ALT enzyme levels by consumer group, substance type, age, and duration of use.

Subgroup	Indicator	Interval (Conf95%)	Std. Error	Mean	Over	Number of Observations	Prob > F	F Value	MS Value	DF	Partial SS	Source
Subgroup 1: Methadone	AST	94.32514-62.92486	7.912511	78.625	53	100	0.0055	8.05	16389.75	1	16389.75	Model 1
Subgroup 2: Opium	AST	62.30951-43.69049	4.691782				0.0055	8.05	16389.75	1	16389.75	Group
									2036.9515	98	199621.25	Residual
									2181.9293	99	216011	Total
Subgroup Analysis	Consumption Type						0.0007	6.22	35150.27	3	35150.27	Model 1
							0.0002	15.43	29077.096	1	29077.096	Group
							0.2034	1.64	29077.096	1	29077.096	Age
							0.0240	5.26	9904.1659	1	9904.1659	Duration of Use
									1883.9659	96	180860	Residual
									2181.9293	99	216011	Total

Subgroup	Indicator	Interval (Conf95%)	Std. Error	Mean	Over	Number of Observations	Prob > F	F Value	MS Value	DF	Partial SS	Source
Subgroup 1: Methadone	ALT	93.65227 - 60.39566	8.266371	77.25	50.71154	100	0.0059	7.93	17579.077	1	17579.077	Model 1
							0.0059	7.93	17579.077	1	17579.077	Group
									2217.6497	98	217329.67	Residual
									23728157	99	234908.75	Total
Subgroup Analysis	ALT						0.0007	6.14	12613.547	3	37840.641	Model 1
							0.0002	15.34	31488.757	1	31488.757	Group
							0.2352	1.43	2929.2189	1	2929.2189	Age
							0.0213	5.48	11258.588	1	11258.588	Duration of Use
									2052.7928	96	197068.11	Residual
									2372.8157	99	234908.75	Total

The first subgroup: methadone
Second subgroup: Opium
Mean estimation
number of obs

4. DISCUSSION

This study aims to compare liver enzyme levels in HCV patients who are chronic users of smoked opium derivatives and oral methadone. This is intended to evaluate and determine these patients' prognosis and treatment response in the diagnostic and therapeutic process.

An analysis of variance was performed to compare AST enzyme levels between the user groups. Given the p-value of 0.0055, which is less than 0.05, the hypothesis is accepted, and we conclude that AST levels in chronic HCV patients using smoked opium derivatives and oral methadone differ. The average AST level in HCV patients using smoked opium derivatives is 53, with a standard deviation of 4.69. The 95% confidence interval for the average AST level in oral methadone users is (62.30, 43.69). Overall, considering the variables of substance type, age, and duration of use, and the model's p-value of 0.007, which is less than 0.05, we conclude that AST levels in chronic HCV patients using smoked opium derivatives and oral methadone differ. The average ALT level in HCV patients using smoked opium derivatives is 50.71, with a standard deviation of 4.88. The 95% confidence interval for the average AST level in oral methadone users is (60.39, 41.027) [19-24].

Matheri et al. conducted a retrospective molecular epidemiology study on August 19, 2005, in Flanders, Belgium, to investigate the molecular epidemiology of hepatitis C among drug users and its association with parameters and risky behaviors, such as gender and drug use. Out of the 162 study patients with HCV RNA-PCR-confirmed hepatitis, 152 (94.4%) reported a history of drug use, either injectable or non-injectable. Among the 152 drug users with hepatitis C, 73.6% were male, and 26.4% were female [25]. The current study's findings were inconsistent with those of the Matheri study.Kharchenko et al. conducted a comparative study in Ukraine to investigate the effects of alcohol and opium on liver function. It was shown that with an increase in opium consumption, destructive and metabolic changes in the liver appear as an increase in liver enzymes [26]. The current study's findings were inconsistent with those of the Kharchenko study.

Woltmann et al. identified 29,018 patients with hepatitis C, of which 18,678 (64.4%) were ultimately included in the final analysis based on study entry criteria. The incidence of newly reported HCV cases was calculated, and demographic data was examined to describe at-risk populations. All age groups showed an increase in positive HCV tests, with the most significant increase occurring in individuals aged 20-29 and 30-39. A slight male predominance (53%) and most white individuals (82%) were observed [27]. The current study's findings were inconsistent with those of the Woltmann study. regarding the non-alignment of average age and slight male predominance.

McNicholas et al. conducted a descriptive-analytic study in 2012 on 175 pregnant female drug addicts. Liver enzyme levels were measured in the study every four weeks during pregnancy and once after delivery. The results showed that Motivational Enhancement Therapy (MET) does not have hepatotoxic effects on pregnant women dependent on drugs. The findings indicate that the highest increase in serum levels of these enzymes was observed in groups that received higher doses of MET, suggesting a dose-dependent drug effect [28]. The current study's findings were inconsistent with those of the McNicholas study.Ahmad Shwaki et al. conducted a cross-sectional case-control study in 2010 titled “The effect of Tramadol consumption on liver damage severity in patients with chronic hepatitis B and C.” Patients in the control group only smoked, while patients in the case group smoked and consumed Tramadol. Sixty patients were included in the hepatitis B group and 60 in the hepatitis C group. The severity of liver damage was determined based on the Histopathological Activity Index. A significant correlation was found between Tramadol consumption and Grade and Stage in both hepatitis B and C groups. In the hepatitis B group, Tramadol consumption was significantly correlated with Grade but not with

Stage. In hepatitis C, the duration and amount of Tramadol consumption were associated with disease stage but not with Grade [24]. The current study regarding the impact of drug abuse on liver damage was inconsistent with the Ahmad Shwaki study.

Overall, with the intervention of variables such as substance type, age, and duration of use, and considering the p-value of the model (0.007, less than 0.05), we conclude that ALT levels in chronic HCV patients using smoked opium derivatives and oral methadone differ.

CONCLUSION

Based on the results of this study, liver enzyme levels in chronic methadone and smoked opium users with HCV are different, with higher liver damage and increased ALT and AST enzymes in methadone users. Therefore, it is recommended that an alternative to methadone be used for addiction treatment in HCV patients, especially those using opium, to improve prognosis and reduce liver damage.

AUTHORS' CONTRIBUTION

The authors confirm their contributions to the paper as follows: Dr. Peyman Astaraki conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Vahideh Yousefvand and Dr. Bahareh Baghchi designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Dr. Maryam Ahadi coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content. All authors reviewed the results and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Permission was taken from the Ethics Committee and Research Committee of Lorestan University of Medical Sciences (IR.LUMS.REC.1400.156).

HUMAN AND ANIMAL RIGHTS

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

CONSENT FOR PUBLICATION

Informed consent was obtained (the under 16 years old was given by a parent or legal guardian).

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

STANDARDS OF REPORTING

Strobe guidelines were followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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