Original Article

Modulation of Blood Lead Level and Liver Function Tests in Iranian Opium Users

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Abstract

Background: Opium users are at risk of lead poisoning. Therefore, this study aimed to compare opium users with healthy controls in terms of blood lead levels (BLLs), blood biochemistry, and liver function tests. **Methods:** A total of 100 people participated in the study. Biological samples (blood and urine) obtained from participants were prepared before analysis for the detection of opium alkaloids (morphine, codeine, papaverine, noscapine,…), amphetamine-type stimulants, and other licit and illicit drugs. Atomic absorption spectroscopy was used to calculate BLLs. We evaluated biochemical parameters and function tests. All statistical analysis was performed by using SPSS. In addition, biochemical parameters and liver function tests were evaluated. **Results:** The BLLs of opium addicts living in Tehran and healthy controls were 18.8 and 7.1 g/dL, respectively. A strong correlation was observed between the route of opium consumption and the average amount of BLL ± SEM (P = 0.037). As compared with the control group, opium users showed a statistically significant (p 0.001) association between the serum levels of the enzyme's aspartate aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, alanine aminotransferase, alkaline phosphatase, and total bilirubin and an increase in white blood cell and hematocrit levels. **Conclusions:** Results of the present study showed that opium users had elevated BLLs in comparison to the control group, which profoundly affected biochemical parameters and liver enzymes.

Keywords: *Biochemical parameters, blood lead level, lead poisoning, liver function tests, opium users*

Introduction

Blood lead level (BLL) is the best indicator of recent lead exposure.[1] It has previously been reported that some drug abusers may display clinical symptoms of lead poisoning.[2] In this respect, opium abuse has been linked to plumbism in some cases. The most widely misused drugs in Iran are opium and its derivatives.[3] In 1973, homemade opium was found to contain lead. Recent studies have shown that there have been few reports of lead poisoning among opium abusers in Iran.[1,4-9] To gain a higher profit, the smugglers and salesmen may add lead to the opium to increase weight. In this regard, opium has become a significant new source of lead poisoning worldwide. Some studies investigating liver function after opium abuse indicated that metabolic changes and liver destruction were seen in opium addicts.[10] Heme synthesis is altered by Pb, which may affect the synthesis of cytochrome P-450 in the hepatic system, this class of enzymes is responsible for the biotransformation of drugs in the liver. The liver is unable to handle lead metabolism to reverse the deleterious effects of lead overexposure, which can also impede a number of enzymatic processes.[11] Within a few hours of liver injury, higher serum concentrations result from the leaking of these enzymes into the serum caused by damage to the hepatocyte membrane.[11] Opium usage damages the liver and stimulates the production of the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), both of which can significantly raise the thymol test. The majority of soft tissues, especially the liver, could be harmed by elevated BLLs.[11] Meanwhile, substance abuse, which is one of the major global problems of the 21st century, is a major public health problem in Iran.[4] In addition to traditional medicine, opium is considered a remedy for many disorders. As a result of the liver's being damaged by lead poisoning, the consumer may experience additional health consequences. It is vital to assess BLL in

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opium users.[12] Few studies have documented lead toxicity among opium users, this study aimed to investigate BLL, and also its effect on biochemical parameters and liver function tests as an indicator of health status in opium users in comparison to healthy subjects in Tehran province, Iran.

Our hypothesis for this study was that opium users might have higher BLL along with hematologic abnormalities and increased liver function enzymes.

Materials and Methods

Participants

Similar studies performed by H Salehi *et al*.[13] and M Amiri *et al*.[14] demonstrated that the sample size in their studies was 44 and 78, respectively, and also PASS V.15 (NCSS, Kaysville, Utah, USA), was used to calculate the needed sample size, and it was estimated 68 cases. based on the inclusion and exclusion criteria at least 50 subjects were needed in each group. A total of 100 blood samples were randomly taken from 50 opium-alive users referred to the Tehran Forensic Toxicology Laboratory, and 50 healthy controls. Samples were selected randomly taken from the Tehran Forensic Toxicology Laboratory during 2018–2021. The study protocol was approved by the Research Ethics Committee of Legal Medicine Organization, Tehran, Iran with the ethical code number (IR.LMO.REC.1396.2).

The study inclusion criteria were the age of ≥18 years old and continuous opium consumption for ≥6 months.

In this study, all patients had a history of opium use and were suspected of having lead poisoning symptoms such as digestive, renal, and mental symptoms. The positive urine toxicology result of opium alkaloids was confirmed by thin-layer chromatography (TLC) method. Similarly, healthy volunteers were randomly chosen from people who had never been exposed to lead or used opium or any other drugs in the same age range as a study group.

The previous history of diseases or any licit or illicit drug use and lead poisoning were assessed during face-to-face interviews. All cases with a history of drug use or medical complications were excluded from the study.

The patients' data were gathered using data collection forms. Potential confounding factors, such as age, gender, education level, city, route, duration, and quantity of opium consumption were evaluated and adjusted one by one utilizing regression techniques. A personal data questionnaire was used to gather details on each participant's lifestyle and health status. A regression analysis was employed to evaluate and adjust each potential confounder, including body mass index (BMI), age, physical activity, and daily diet.

Urine analysis for the qualitative determination of opium alkaloids and other drugs

Forty mL of urine samples were collected from opium users and control subjects. Acon immunochromatography and TLC techniques were used to detect opium alkaloids in urine specimens as screening high-performance liquid chromatography (HPLC) and gas chromatography/mass spectrometry (GC/MS) techniques as confirmatory methods.

TLC sheets (20 × 20), coated with a 0.25-mm layer of silica gel and an ultraviolet fluorescence indicator ALUGRAM® Xtra SIL G SIL UV254 (Macherey-NAGEL GmbH, Düren, Germany).

Acid hydrolysis was performed for the cleavage of drug conjugates in urine samples. To perform acid hydrolysis, a urine sample's pH was adjusted by hydrochloric acid to 1–2 and then incubated at 60°C for three h. The medium's pH was adjusted from 8.5 to 9.0 to extract opium alkaloids. Chloroform: isopropanol (8:2 v/v) was used to extract opium alkaloids from aqueous phase. Organic layer containing opium alkaloids was separated and evaporated to dryness. Residues were reconstituted in 10 μL of methanol and analyzed using the TLC method.

Analysis of all other drugs including narcotic drugs was performed using GC/MS and HPLC by an assay technique described previously.[15,16]

Instrumentation

For the extraction and detection of amphetamine, methamphetamine, and other psychoactive substances, including tetrahydrocannabinol, 3,4-methylenedioxymethamphetamine, tramadol, barbiturates, benzodiazepines, tricyclic antidepressant, buprenorphine, methadone, cocaine, sensitive methods including dispersive liquid-liquid extraction, liquid-liquid extraction, HPLC, and GC/MS were used for the analysis of in urine samples. The extracts were examined using GC/MS (Scion, 30 mm 0.250 m. 0.25 m, SS), HPLC (KNAUER GmbH, Berlin, Germany), and C18 column (250 mm 4.6 mm, particle size: 5 m).

Measurement of the blood lead level

BLL was determined using an atomic absorption spectrometer (Varian SpectrAA-600-USA) as described by a previous study.[11] A 50 μL of Ethylene diamine tetra acetic acid (EDTA) blood sample that had been diluted with 450 μL of Triton-X 100 was placed inside each auto-sampler curette. Lead analysis was performed by the automated digestion, drying, burning, and atomization of the sample. Absorbance measurements were made at 680 nm.

Determination of biochemical parameters

Ten mL of blood samples with EDTA pre-coated test tube were used for biochemical analyses, and also the serum samples were separated after centrifuging the venous blood samples at 3000 rpm for 5 min. Using commercial kits (Roche), a cell counter and an auto-analyzer (Roche - Hitachi MODULAR Analytics, Japan) the levels of white and red blood cells (WBC, RBC), mean corpuscular hemoglobin (MCH), total bilirubin, and total protein (Roche), total protein, hemoglobin (Hb), aspartate aminotransferase (AST), alkaline phosphatase (ALP), hematocrit (HCT), gamma-glutamyl transferase (GGT) alanine aminotransferase (ALT), total bilirubin, and lactate dehydrogenase (LDH).

Statistical analysis

All statistical analysis was performed using SPSS version 24 (SPSS, Inc., Chicago, IL, USA). Mann-Whitney, Chi-square, and Kolmogorov-Smirnov and multiple regression tests, Kruskal-Wallis, and Spearman correlation coefficients were used to identify the association between the study variables. P value < 0.05 was considered statistically significant.

Results

A total of 100 cases (including 50 opium users and 50 controls) participated in the study. Overall, all samples were screened using the Acon rapid test, TLC, HPLC, and GC-MS. Positive samples for drugs other than opium alkaloids were excluded [Figure 1] because of the effects of other drugs on blood biochemical parameters, and liver enzymes as confounding factors.

All 50 samples were positive for opium by immunochromatography, and TLC and negative for other drugs by HPLC and GC/MS.

Of 50 patients, 11 (22.9%) were females and 39 (78%) were males. The demographic parameters of the participants (such as age and gender) are exhibited in Table 1. No significant differences were observed between opium users and controls for age and gender, ($P > 0.05$) [Table 1].

The mean BLLs of the subjects are displayed in Table 2. The mean BLLs were 18.8 ± 12.6 µg/dL and 7.1 ± 0.7 µg/dL for the opium users, and controls, respectively [Table 2].

The longest duration of opium consumption was more than 10 years. The highest mass of consumed opium was 1.5 g per day, and also inhalation was the most common route of consumption (62%). The quantity of opium consumed daily and the length of time was not significantly different in all BLLs ($P = 0.212$) (0.471).

However, a significant correlation was detected between the BLLs and the route of opium consumption ($P < 0.037$). Comparing the characteristics of different BLLs and opium users revealed that Subjects that inhaled opium had significantly lower BLLs than oral opium users ($P = 0.024$) and oral/inhaled opium consumers ($P = 0.037$) [Table 3].

Opium users significantly showed an increase in the activities of liver function test results (serum AST, ALP, ALT, GGT, LDH, and bilirubin) ($P < 0.001$).

Table 4 displays the outcomes of biochemical tests. Although all participants' WBC and HCT levels were within the normal range, the WBC and HCT levels of opium users 1 were considerably lower than those of controls ($P = 0.026$ and $P = 0.001$, respectively). There were no significant differences between the groups in RBC, Hb, mean corpuscular volume (MCV), and MCH levels ($P > 0.05$).

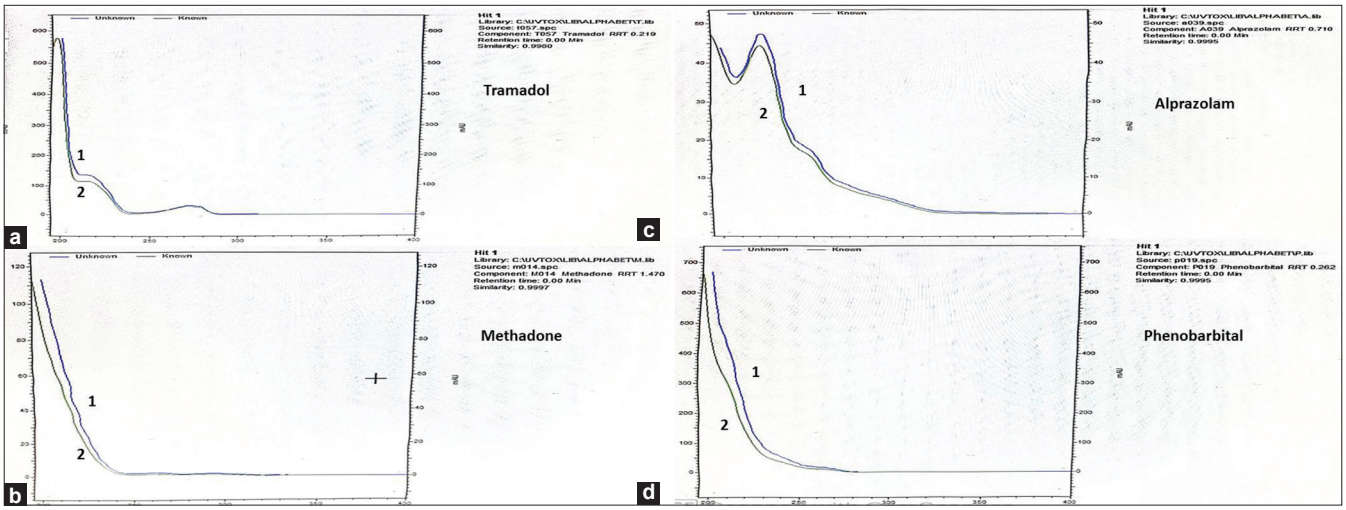

Figure 1: HPLC chromatogram from absorbance measured with diode-array detector (DAD) between 220 and 400 nm. The 3D plot from HPLC-DAD allowed the peak for tramadol, methadone, phenobarbital and alprazlam to be clearly identified in the urine sample of a multidrug user case. 1). Standard and 2). Urine spiked with (a). Tramadol (b). Methadone (c). Alprazlam and (d). Phenobarbital. The extracts were analyzed using HPLC (KNAUER GmbH, Berlin, Germany), C18 column, flow: 1 ml/min, Run time: 40 min and detector type: DAD (Smartline 2800)

Discussion

Two-third of all fatal poisonings had opiates or opioids as the primary toxic agent, with heroin or morphine, being the leading cause of these deaths.[15] As a result, forensic and clinical toxicology professionals have deemed the analysis of opioids in biological materials to be a crucial concern. In the present study, all samples were screened using the Acon rapid test and TLC.

Positive samples for opium were evaluated by TLC, and also other drugs in urine samples were evaluated by HPLC and GC/MS.

Most types of various analytical techniques used for both the measurement and determination of narcotics were HPLC and GC-MS, which are practically and technically deemed as the most common technique used to determine the presence of narcotic substances in forensic toxicology practice.[16] HPLC can eliminate inaccurate TLC technology and avoid potential interference for proving the number of substances in the mixture. It has demonstrated the number of narcotics within the sample through the number of peaks in the chromatogram.[17]

We found that BLLs were significantly increased in opium users compared to the controls. Our findings are consistent with those found by Amiri *et al*. reporting significant differences between addicts and non-addicts in terms of BLLs.[14] A systematic review also indicated that the use of opium might raise the levels of circulating lead. Additionally, opium users who took it orally had much greater BLLs than those who utilized other route types.[12]

In this study, the most common route of consumption was inhalation. Another study[18] demonstrated that the majority of users who inhaled opium reflected the popularity of this method in Iran, which agreed with our study. In the present study, one of the elements determining the BLLs in opium users was the kind of opioid that was taken. The respiratory tract, with an average absorption of roughly 40%, is one of the main routes for lead exposure (to reach the bloodstream). In this regard, we found that BLLs were reduced in opium inhalers. This might be because of the wafoor, a tubular instrument used to inhale opium, has some lead built up in it, preventing the lead from getting into the lungs. The results of our univariate and multivariate analyses did not differ. Adjusted and crude opium effects for both groups demonstrated a confounding influence of the adjusted effects like city, on the link between BLLs and opium use. The mean BLLs in opium users living in Tehran were significant, suggesting that opium users living in Tehran are gradually affected by heavy metal lead owing to the indirect use of lead in opium. Therefore, this claim requires future studies with a larger sample size.

Table 1: Comparison of demographic parameters of opium users and controls (*P*>0.05 control group versus opium users)

Variables	Opium users *n* (%)	Healthy Controls *n* (%)	*P*
Age (y)			
<40	39 (78)	41 (82)	
41-50	2 (4)	2 (4)	0.784
51-60	2 (4)	3 (6)	
<60	5 (10)	4 (8)	
Gender			
Male	11 (32)	16 (32)	0.260
Female	39 (68)	34 (68)	

P<0.05 versus control and opium users

Table 2: BLLs opium users living in Tehran and healthy controls

City	Group	*n* (%)	Mean	Standard deviation	Median	*P*
Tehran	Opium user	25 (50)	18.8	12.6	15.2	>0.001
	Healthy control	25 (50)	7	10.7	2	

P<0.05 versus control and opium users

Table 3: Comparative variations in BLLs of opium users

Variables	Opium users *n* (%)	Blood lead level (mg/dl), mean	Standard deviation	Median	Intermediate range	*P*	Coefficient (*r*)
Route of use							
Oral	9 (18)	18.1	10	16.2	16.3	0.037	-
Inhalation	31 (62)	10.4	9.6	6.5	10		
Oral + Inhalation	10 (20)	20.2	14.9	14.9	28.3		
Quantity of consumption (g/day)							
0.5>	29 (58)	15.2	11.5	12.3	18.9	0.417	-0.117
1-0.5	11 (22)	6.3	3	5.5	5.2		
>1.5	10 (20)	17.7	14.7	14.5	24.7		
Duration of consumption (year)							
≥0.5	25 (50)	12	11.5	7.2	9.2	0.212	0.179
10-6	13 (26)	12.7	8.2	14.2	11.9		
>10	12 (24)	18.5	14.1	15.5	26.1		

P<0.05 versus opium users

Table 4: The whole blood biochemical parameter in the serum levels of opium users and controls

Parameters	Opium users					Healthy Controls				*P*, Univariate test	Multiple regression results		
	Normal range	Mean	Standard deviation	Median	Intermediate range	Mean	Standard deviation	Median	Intermediate range		Regression results	Standard error	*P*
Pb (µg/dl)	20>	13.7	11.5	9.05	13.8	4.8	7.9	2	3.6	0.001	4.8	1.4	0.001
RBC (mil/cumm)	6-0.3 3.9	5.0	0.8	5.1	1.1	5.1	0.7	5.3	1.1	0.485	0.11	0.15	0.485
WBC (×1000/µl)	11-4	6.9	1.3	7	1.4	7.4	0.7	7.4	0.9	0.002	0.47	0.21	0.026
Hb (g/dl)	17-12	13.5	1.6	13.7	2.1	13.5	1.1	13.6	1.3	0.884	0.04	0.34	0.90053
HCT (%)	53-36	41.9	5.1	41.3	8.1	44.8	3.2	45.1	4.2	0.001	3.09	0.83	0.001
MCV (fl)	100-80	83.4	2.4	83.0	3.2	84.2	2.2	84	4	0.071	0.77	0.46	0.096
MCH (pg)	32-27	28.1	1.6	28	2	28.2	1.7	28	2	0.958	0.05	0.32	0.877
AST (U/L)	45-5	33.8	13.4	35.5	22.5	22.7	9.9	19.5	11	0.001	11.17	2.36	0.001
ALT (U/L)	40-1	36.7	16.6	35.7	22	25.5	9.5	25	12.7	0.001	11.09	2.71	0.001
ALP (U/L)	270-50	240.2	202.3	229.7	108	136.5	50.8	146	71	0.001	103.7	29.5	0.001
LDH (U/L)	480≤	321.8	157.3	313	211	203	85.3	198	99.5	0.001	178	32.5	0.001
GGT (U/L)	30≤	25.8	8.3	25.5	13	17.6	5.9	15.5	7.2	0.001	8.2	1.4	0.001
Bilirubin total (mg/dl)	1-0.2 0.1	0.79	1.21	0.60	0.43	0.54	0.24	0.6	0.4	0.116	0.38	0.18	0.041
Total Protein (g/dl)	8-0.8 6.6	7.13	0.53	6.90	0.70	7.23	0.58	6.9	0.7	0.647	0.09	0.11	0.388

P<0.05 versus control and opium users

The WBC and HCT levels were within the normal range in all subjects. They were significantly higher in the opium users with high BLLs. A significant increase in WBC and HCT levels needs to be further investigated. Previous studies have reported the connection between BLL and WBC levels in Tehran,[19] Canada,[17] and Iran.[20] However, no significant differences were found between the groups of RBC, Hb, MCV, and MCH. These results were consistent with those of a previous study conducted on opium users in Saudi Arabia.[21]

In the current study, compared to the control group, opium users had considerably higher findings from tests measuring the activities of the liver (serum ALP, AST, GGT, ALT, and bilirubin levels).

Our results were agreed with those found by Allouche investigating the effect of long-term exposure to low or moderate lead acetate on growth, serum lipid profile, and some biochemical parameters in an experimental model. They reported changes in serum LDH, ALP, AST, and ALT activities in well-nourished rats.[9] For the diagnosis and treatment of liver diseases, serum biochemical testing can be very helpful. Utilizing such tests frequently may improve the ability to detect liver disorders. It was shown that lead exposure induced liver histopathological alterations in rats and damage in human liver carcinoma cells *in vitro*. Lead-induced liver damage is an uncommon finding and has anecdotally been reported.[22] The state of hepatic functions has been demonstrated using ALT and AST levels. Increased ALT and AST levels were found to be similar to the previous study.[23] In addition, nephrotoxicity and hepatotoxicity of morphine abuse have been reported.[24-28] The levels of bilirubin and GGT can also be considered as an indirect indicator of the level of hepatic function. There is a correlation between high serum levels of bilirubin and the lack of balance between production and conversion followed by excretion of the bilirubin. A significant association was found between BLL, GGT and bilirubin. Levels in the study of Dobrakowski *et al*.,[29] suggest that in lead-exposed adults, serum bilirubin levels were significantly elevated. Additionally, a comparable outcome was seen in a study conducted on mice.[29,30]

Ye *et al*.,[28] reported that children with lead poisoning had significantly lower serum bilirubin levels. In contrast to our findings, Wu MT *et al*.[31] found no significant variations in the GGT between the industrial employees and control groups. Bilirubin levels and these parameters did not correlate with the BLLs. This controversy may be caused by different routes and sources of human lead exposure or quantity of lead which makes histopathological changes in the liver and results in changes in biochemical parameters related to the severity of histopathological changes.[32]

LDH level increases in cases of liver injury, hemolysis, and myocardial infarction. To screen liver disease, ALP and LDH have also been employed. Users had significantly higher ALP and LDH levels as compared with controls. There was a strong association between ALP, LDH and BLLs in this study. Similar findings have been reported on the connection between BLL and LDH, ALP levels in Turkey[33] and Algeria.[9] Exposure to lead can slow the metabolism of intermediaries, which can raise LDH levels. Furthermore, it has been demonstrated that lead exposure raises ALP and LDH levels, resulting in hepatorenal damage. These key indicators, which were substantially connected with lead poisoning, included abnormal liver enzyme tests that might have been brought on by liver tissue antioxidant/oxidative cycle disruptions or by the antioxidants' depletion in the cells.[34]

Conclusions

The results of the current study confirmed the role of elevated BLLs in opium users as a cause of the change in the parameters of liver function tests. Opium can be inhaled or ingested orally, resulting in lead poisoning in long-term users of opium tainted with lead.

Opium consumption was significantly associated with city, route, duration, and quantity of consumption. Moreover, lead can cause liver damage, raising AST, ALP, ALT, GGT, LDH, bilirubin, WBC, and HCT levels in opium users. The results of this study showed that there is still a need for more understanding of the effects of the different preparations of opioids on biochemical factors.

Study limitations

Our study should be interpreted within the context of its possible limitations. There were not enough pure morphine samples in our opium group. Most addicts used multiple drugs, such as amphetamine, methadone, and tramadol that might affect their blood biochemical parameters and liver enzymes; therefore, most addicts were excluded from the study. This problem prolonged the sampling process and included people in the study.

Ethics approval and consent to participate

The Ethics Committee of the Legal Medicine Organization of Iran approved the study protocol. With the ethical code number (IR.LMO.REC.1396.2). The written informed consent form was read and signed by each participant following the general principles outlined in the Declaration of Helsinki.

Authors' contributions

ME is the researcher who wrote the manuscript with support from FH who is a MD in psychiatry, and he also found and monitored the patients. MK, MC, MF, RA, and MT were involved in sampling and testing of cases in the laboratory. RG, a Prof of statistical medicine, analyzed the data. MN and BN were involved in project implementation. MA, the corresponding author, was the owner of the idea and the supervisor of the whole project. All authors contributed

to the development of the article and participated in the review process.

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Conflicts of interest

There are no conflicts of interest.

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