Review Article

Lead Poisoning in Opium Abuser in Iran: A Systematic Review

Abstract

Substance abuse and its consequences are major health hazards in the world. Opium addiction is a common form of substance abuse in Iran. Adulteration of illegal substances in the process of production and distribution of the drug in black market with many types of materials have been reported. One of the main goals of the adulteration of illegal substances is cutting of the substance for deal and increase of the weight for more benefit. However, adding of adulterating agents to illegal drugs could be considered as a cause of nonspecific and rare toxicity during substance abuse. Although the presence of lead in street-level heroin, marijuana, and amphetamines has been reported from some countries previously, recently, several reports suggested lead poisoning in Iranian opium addicts. Adulteration of opium with lead is a new source of lead poisoning in Iran in which the opium abuse is frequent and it could be a new health problem in the future. In this regard, evaluation of blood lead level would be important for early diagnosis of lead poisoning in opium addicts.

Keywords: *Iran, lead, opioid-related disorders, opium, poisoning*

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Introduction

Lead is a bluish-gray metal and highly toxic element. Its properties such as corrosion resistance, density, and low melting point make it a familiar metal with high applications in the industry.[1,2] It can induce acute and chronic poisoning in human.[1] Lead is considered as a toxic substance affecting multiple organ systems.[3] Its poisoning can be due to occupational or environmental exposures, for example, car exhausts, contaminated food, industrial emission, and contaminated soil.[4] Ingestion, inhalation, or dermal exposure to the lead contamination sources can cause notable poisoning.[4]

Clinical presentations of lead toxicity are nonspecific including abdominal pain, anorexia, constipation, myalgia, decreased libido, irritability, seizure, and anemia.[3] Abdominal pain in lead poisoning can be misdiagnosed as an acute abdomen.[5]

Nowadays, the incidence of acute lead poisoning has declined, but the chronic lead poisoning still exists in various parts of the world.[2] The majority of elevated blood lead levels (BLLs) in adults come from occupational and industrial exposures.[6,7] Lead exposure is usually considered when a patient's history is remarkable to well-known sources of lead such as in occupational and industrial settings. However, unusual causes of lead intoxication have been described. One of the uncommon sources of lead poisoning is lead-adulterated illegal substances abuse such as marijuana and methamphetamine.[8-10]

Substance abuse is a major problem of public health in Iran.[11,12] Opium and its derivatives is the most common drug that is abused in Iran.[11] Recently, few reports about lead poisoning in opium abusers in Iran have been reported.[13-18] In addition, researchers reported the presence of lead in opium in the southeast of Iran.[19] It seems that the lead is present as impurities and adulterants in illicit opium, which smuggled and distributed in Iran. In this article, we reviewed the reports of lead poisoning in opium abusers in Iran.

Methods

A literature search of online databases (PubMed, Web of Science, Google Scholar, and Scopus) for studies investigated lead poisoning in opium abusers in Iran was performed.

Search criteria

The search terms were "opium/opium abuse," and "lead poisoning/toxicity" or

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"lead-contaminated opium." The data were collected from March 2000 to November 2016. There were no language restrictions. All types of papers were included. We also reviewed the reference lists of identified publications and abstract book of national congresses for additional studies. The title and abstract of each article were reviewed to make a decision for eligibility of the paper. Full text of all eligible papers was obtained. Finally, 18 articles have been included in this review.

Results

Lead poisoning in opium abusers

Beigmohammadi *et al.* reported a 40-year-old male with opium addiction history with a headache, nausea and abdominal pain, and weakness in his lower and upper extremities without a definitive diagnosis who was admitted in Intensive Care Unit (ICU). He did not have an occupational lead history in his past medical history. He had anemia, slightly elevated liver function tests, total bilirubin, and erythrocyte sedimentation rate. Electromyography and nerve conduction velocity results and neurologic examination were abnormal. His BLL was more than 200 μg/dL. He was treated with British Anti-Lewisite (BAL) and calcium disodium edetate $CaNa_2EDTA$. Following ICU discharge, he was quadriplegic although BLL was decreased and all paraclinical findings were normal.[15]

Hayatbakhsh Abbasi *et al.* conducted a cross-sectional study to compare the serum lead levels between opium addicts (n = 50) and nonaddicts (n = 43). They were matched with sex and age. The serum level of lead in opium addicts was higher than nonaddicts.[16]

In another study which has been conducted by Salehi *et al*., they analyzed the BLL in opium addicts (n = 22) who used oral opium and control group (n = 22) which was matched with for age and sex. The BLL in opium addicts had a range of 7.2–69.9 μg/dL (mean of 21.9 ± 13.2 μg/dL). In control group, BLL was 4.1–17.4 μg/dL (mean of 8.6 ± 3.5 μg/dL). The result was statistically significant ($P < 0.0001$). In the patient group, BLL had a significant correlation with the amount of ingested opium ($r = 0.65$, $P < 0.01$). However, there was no significant correlation with duration of opium ingestion in the patient group. They concluded that screening of BLL should be considered in the treatment of opium addicts.[20]

Masoodi *et al.* (2006) showed that lead poisoning in three patients presented with diffuse abdominal pain, anemia, constipation, nausea, vomiting, and abnormal liver function tests. A history of oral consumption of opium was presented in all of the patients, and none of them reported known occupational lead exposure. Lead poisoning was confirmed by analysis of BLL. Ingestion of lead-contaminated opium was the cause of poisoning.[13]

Salman-Roghani and Foroozan reported a 46-year-old opium-addicted man with hepatobiliary tract problems. He complained of abdominal pain, constipation, weakness, and neurologic abnormalities (tremor and proximal weakness). BLL was 90 μg/dL, and the patient was treated with the diagnosis of lead toxicity.[21]

Verheij *et al.* described a case of the 40-year-old Iranian man anemia and abnormality in liver function tests with severe abdominal pain, In his past medical history, he was suffering from multiple sclerosis. The patient used opium as a painkiller, regularly. Basophilic stippling of erythrocytes proposed lead poisoning. In this patient, the probable source of poisoning was adulterated opium. BLL were strongly elevated (86 μg/dL). The authors showed lead-induced hepatotoxicity in the case. In the liver biopsy, pathologic findings of hepatotoxicity such as active hepatitis lymphocytic cholangitis, with steatosis, cholestasis and hemosiderosis have been reported in the patient. After chelating therapy, liver enzymes returned to normal, suggesting reversibility of the histological findings.[22]

Soltaninejad *et al.* in a descriptive and retrospective study presented 25 cases of lead poisoning who were admitted to a referral poison center in Tehran between the years 2002 and 2007. In seven patients, opium addiction was the only source of lead poisoning. None of them had a well-known occupational exposure to lead. The average age of the patients was 38.7 ± 9.3 years and the average BLL was 109 ± 37.6 μg/dL. Inhalation was the route of opium abuse in 4 patients. Others abused opium orally.[23]

Froutan *et al.* reported opium addicts with abdominal pain who were presented to the gastrointestinal center of a referral hospital in Tehran during 2008. Patients who had occupational exposure to lead were excluded from the study. During this period, 42 patients (all male) with an average age of 46.9 ± 10.1 years were included in the study. Average BLL was 51.17 ± 27.96 μg/dl. A total of 22 patients (52.6%) had lead poisoning. A significant relation was found between lead poisoning and mode of opium abuse. The relation between lead poisoning and duration of opium addiction was not observed. However, a statistically significant relation was found between lead intoxication and abnormal liver function tests, urine tests, electrocardiogram, presence of basophilic stippling, and hyperuricemia.[5]

Meybodi *et al.* demonstrated that of the 240 patients diagnosed with lead poisoning, 25 patients admitted to opium use. There were 24 (96%) men and one (4%) woman. The average age of the patients was 41.8 ± 13.5 years. The duration of addiction to oral opium differed widely (range 3 months to 40 years). BLL were 145 ± 61 (range: 61–323) μg/dL. There was no significant statistical correlation between the duration of addiction and BLL in addicted patients ($r = -0.142$, $P = 0.54$). The most common complaints were anorexia (96%), abdominal pain (92%), weight loss >10% within a 2-month period (84%), constipation (88%), and nausea (56%). The most common musculoskeletal complaint was

muscle weakness (92%). Other complaints included wrist drop (4%), pain in the extremities (88%), paresthesia (56%), and reduced vision (20%) and hearing (8%). Three (12%) patients initially presented with acute abdomen (bowel obstruction and peritonitis).[24]

Amiri and Amini evaluated the BLL of 39 Iranian opium addicts and made a comparison with healthy individuals as a control group in a hospital in Tehran. All the cases were male. The addicts were used opium orally or by inhalation. The mean age was 48.6 ± 7.3 years. The control group (39 individuals) was matched with the addicts with regard to age and sex and with a mean age of 44.8 ± 5.6 years. The mean BLL was found to be significantly lower (P = 0.0001) in control group (16.70 ± 12.51 μg/dL) compared to addicts (57.04 ± 46.03 μg/dL). There was a significant difference (P = 0.0451) in BLL according to age. Furthermore, a tendency (P = 0.048) toward increasing BLL with respect to body mass index (BMI) was observed due to opium abuse, but there was no significant variation between BLL and BMI when the control group was considered (P = 0.35).[25]

Mokhtarifar *et al*. reported a 55-year-old man presented to the emergency department with abdominal pain, icterus, high serum alkaline phosphatase levels, and normocytic anemia. He had opium abuse history for 20 years. Clinical and paraclinical findings including the Burton's sign and generalized ileus on abdominal X-ray have been observed. BLL was 150 μg/dL. Investigation of the patient's history failed to reveal any exposure to lead. Magnetic resonance imaging and abdominal ultrasonography were performed for rule out the other reasons of cholestasis. Liver biopsy showed focal canalicular cholestasis and mild portal inflammation. The patient had severe nausea, vomiting, and a single generalized tonic–colonic seizure 4 days after admission. Neurologic evaluations including brain computed tomography scan, and magnetic resonance imaging, and magnetic resonance venography were normal. The patient was treated with $CaNa_2EDTA$ and BAL for five days. The patient's liver biochemical tests abnormality recovered. Gastrointestinal presentations subsided, and the patient was discharged with good condition.[26]

Domeneh *et al.* in a cross-sectional study among 86 opium addicts who were referred to five detoxification centers in Tehran, reported that BLL was higher in oral opium-dependent group (11.75 ± 6.06 μg/dL) than inhalation opium addict (7.07 ± 3.61 μg/dL) and healthy (6.05 ± 1.83 μg/dL) groups.[27]

Khatibi-Moghadam *et al.* reported that the mean value BLL in 40 opium addicts was 7.14 ± 1.41 μg/dL compared to 5.42 ± 1.46 μg/dL in healthy control group. The mean value of urine lead level was 2.62 ± 0.83 μg/dL and 2.50 ± 0.76 μg/dL in patient and control groups, respectively. They showed a significant correlation between BLL with duration of opium addiction.[28]

Azizi *et al*. reported a lead-intoxicated case in a 46-year-old Iranian man who resident in the UK with opium addiction history. He had a 4-day history of colicky abdominal pain and constipation and several weeks of irritability and malaise. He had smoked 10 g of opium per week for a year and a half. On examination, he had abdominal pain, nausea, vomiting, diffuse abdominal tenderness, and fecal loading. Furthermore, hemolytic anemia and basophilic stippling have been shown in hematologic tests. The patient's serum lead concentration was substantially elevated. After chelation therapy, he has recovered clinically and biochemically.[29]

Lead poisoning due to abuse of lead-contaminated opium

Soltaninejad *et al.* reported a fatal lead poisoning in a 27-year-old man with 2 years of opium addiction history. Lead poisoning was confirmed by analysis of BLL (150 μg/dL) and clinical and postmortem autopsy findings. Lead content has been determined in opium sample which ingested by the decedent by atomic absorption spectrophotometer as 5.6%w/w.[30,31]

Fatemi *et al.* reported a lead poisoning in a 25-year-old man with 6-year history of addiction to oral and inhalation opium. He presented with gastrointestinal presentations such as abdominal pain, nausea and vomiting, severe weight loss, generalized bone pain, and jaundice without hepatosplenomegaly and lymphadenopathy. Pallor and jaundice were observed in his mucosa and bluish pigmentation was evident at the gum-teeth line. Liver enzymes and indirect bilirubin increased. Hemolytic anemia without autoimmune origin and erythroid hyperplasia has been shown in bone marrow biopsy. The serum lead level was 350 μg/dL. Furthermore, the lead was detected in opium sample that the patient used. The patient was treated with standard $CaNa_2EDTA$, and BAL and symptoms were eliminated during 2 weeks after chelating therapy.[14]

Aghaee-Afshar *et al.* analyzed the lead content in ten opium samples which were selected randomly from the opium seized by Police Department in Kerman province (South-east of Iran) by atomic absorption spectrophotometer. The mean concentration of lead in the samples ± standard error of mean was 1.88 ± 0.35 ppm. The minimum and maximum lead concentrations in the samples were 0.7308 ppm and 3.5255 ppm, respectively.[19]

Jalili and Azizkhani reported a lead poisoning case in a 32-year-old man with opium addiction who presented to the emergency department with lower abdominal pain and constipation. In physical examination, he had mild abdominal tenderness and gingival discoloration. Laboratory findings showed a mild hypochromic, microcytic anemia with basophilic stippling of the erythrocytes. The BLL was 50 μg/dL and diagnosis of lead toxicity was made and the

Table 1: Clinical studies relevant to lead poisoning due to opium addiction in Iran

Study	Number of cases	Gender of patient(s)	Age (mean±SD) (year)	Main clinical presentations	Route of opium abuse	Duration of opium addiction (year)	Blood lead level (µg/dL)
Soltaninejad *et al*. (2004)	1	Male	27	Nausea, vomiting, abdominal cramps, seizure, anemia	Oral	2	150
Fatemi *et al*. (2008)	1	Male	25	Abdominal pain, nausea, vomiting, severe weight loss, generalized bone pain, jaundice, bluish pigmentation of gum, hemolytic anemia	Oral and inhalation	6	350
Beigmohammadi *et al*. (2008)	1	Male	40	Headache, nausea, abdominal pain, weakness in lower and upper extremities, peripheral neuropathy, respiratory failure, anemia	Oral	NR	>200
Hayatbakhsh Abbasi *et al*. (2009)	50	Male (34) Female (16)	22.18±39.74	-	Inhalation	NR	3929.35±147.67
Salehi *et al*. (2009)	22	Male	38.8±6.7	-	Oral	2-5	21.9±13.2.
Masoodi *et al*. (2009)	3	Male	45.3±9.4	Nausea, vomiting, abdominal pain, constipation, liver enzymes elevation, anemia	Oral	NR	71.16±24.48
Jalili *et al*. (2009)	1	Male	32	Abdominal pain, anorexia, constipation, gingival discoloration, anemia, elevation of liver enzymes	Oral	NR	50
Salman-Roghani and Foroozan (2009)	1	Male	46	Nausea, abdominal cramps, anorexia, loss of weight, general weakness, tremor, elevation of liver enzymes, anemia, polyneuropathy, hypertension	Oral	10	90
Shariat Moharari *et al*. (2009)	2	Male	27 and 68	Abdominal pain, anorexia, constipation, weakness, icter, delirium, hyperirritability, tremor, anemia, loss of consciousness, coma	Oral	NR	154 and 180
Verheij *et al*. (2009)	1	Male	40	Severe abdominal pain, abnormal liver function tests, anemia, cholestasis, elevation of liver enzymes	Oral	NR	86
Soltaninejad *et al*. (2011)	7	Male	38.7±9.3	Abdominal pain, nausea, vomiting, paresthesia, fatigue, anemia, constipation, delirium, seizure	Oral and inhalation	NR	109±37.6

Contd...

Table 1: Contd...

Study	Number of cases	Gender of patient(s)	Age (mean±SD) (year)	Main clinical presentations	Route of opium abuse	Duration of opium addiction (year)	Blood lead level (μg/dL)
Froutan *et al*. (2011)	42	Male	46.9±10.1	Lead line at gum-tooth line (19%), electrocardiographic evidence of conduction delays (14.3%), cataract patients (28.6%), hypertension (23.8%), anemia (42.9%). Rise in liver enzymes (19%)	Oral (71.4%) and inhalation (28.6%)	17±10	51.17±27.96
Aghaee Meybodi *et al*. (2012)	25	Male (24) Female (1)	41.8±13.5	Anorexia (96%), abdominal pain (92%), weight loss (84%), constipation (88%), nausea (56%), muscle weakness (92%). Wrist drop (4%), pain in the extremities (88%), paresthesia (56%), reduced vision (20%), and hearing (8%), 12% patients who initially presented with acute abdomen (bowel obstruction *n*=2 and peritonitis *n*=1)	Oral	3 months to 40 years	145±61
Amiri and Amini (2012)	39	Male	48.6±7.3	-	Oral and inhalation	NR	57.04±46.03
Mokhtarifar *et al*. (2013)	1	Male	55	Abdominal pain, icterus, constipation, postprandial nausea and vomiting, lead line at gum-tooth line, anemia, elevation of liver enzymes, seizure	Oral	20	150
Domeneh *et al*. (2014)	86	Male	33.5±16.51	Anemia	Oral, inhalation	NR	11.75±6.06 in oral opium-dependent group and 7.07±3.61 in inhalation opium-dependent group
Khatibi-Moghaddam *et al*. (2016)	40	35 male and 5 female	43±10	NA	Oral, inhalation	17±10	7.14±1.41
Azizi *et al*. (2016)	1	Male	46	Abdominal pain, nausea, vomiting, abdominal tenderness, irritability, malaise, hemolytic anemia with punctate basophilic stippling, Burton's line, elevation of serum lead level	Inhalation	1.5	-

NR=Not reported, SD=Standard deviation, NA=Not available

patient was treated with 2,3-dimercaptosuccinic acid. His signs and symptoms subsided over the next week and he was discharged. Analysis of the used opium sample showed 35.2 mg of lead per 100 g of opium.[17]

Moharari *et al.* reported two cases (Iranian father and son), with severe lead poisoning due to opium addiction. The patients have been hospitalized with regard to neurological symptoms (unconsciousness, delirium, and hyperirritability), gastrointestinal (icter, abdominal pain) and anemia. The older patient (68-year-old man) showed the neuropathy and electro encephalography symptoms including paralysis and absent deep tendon reflexes and low level of consciousness. The patients' BLL indicated a high level of lead in both of them (≥150 μg/dL). Furthermore, the used sample of opium was sent to the laboratory, and analysis of lead in the sample showed a higher lead content. One of the patients died due to cardiovascular collapse.[32]

Table 1 summarizes clinical studies relevant to lead poisoning due to opium addiction in Iran.

Discussion

Although lead poisoning in industrial and occupational settings has decreased, the new forms of nonoccupational lead poisoning have increased. The presence of heavy and toxic metals such as arsenic in opium,[33-36] lead, and thallium in heroin samples as impurities and adulteration has been reported from some countries.[37-41] There are a few reports about lead poisoning due to abuse of lead-contaminated opioid worldwide, and in recent years, lead poisoning in opium addicts have been reported from Iran.

In this article, we reviewed 20 documents; from which, 18 studies reported 324 cases of lead poisoning in opium abusers in Iran during 2004–2016. According to these researches and medical evidences, it could be concluded that illegal opium samples in Iran have been contaminated with lead. It may be due to adulteration of opium by dealers, salesmen, and smugglers during the opium preparation and distribution in the black market to increase the weight of opium for more profit. The studies showed that there is a statistically significant correlation between BLL and route of opium abuse. Higher BLL was observed in patients with oral opium abuse. Furthermore, there is a significant correlation between BLL and amount of opium abuse. There are controversies with regard to the correlation between BLL and duration of opium abuse.

From this view, as a new health problem, lead poisoning should be considered in illegal opium abusers, mainly oral consumption, in Iran and other countries in which the opium abuse is frequent. As clinical manifestations of lead poisoning are nonspecific and may be misdiagnosed with other pathophysiological conditions, public health experts should be notified and conduct an assessment of the risk of lead poisoning in opium addicts.

Conclusions

Screening of BLL would be helpful for early diagnosis and treatment of lead poisoning in opium abusers to prevent complications of chronic lead poisoning.

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Conflicts of interest

There are no conflicts of interest.

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