The Outbreak of Lead Poisoning in Opium Users: Presentation and Chelation Therapy

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Abstract- Recently, there have been a few reports of an outbreak of lead poisoning due to opium contaminated with lead in Iran. This study aimed to evaluate the clinical features of lead toxicity in opium abusers, and response to oral chelation therapy based on the severity of poisoning. One hundred thirty-three chronic opium users with a diagnosis of lead poisoning were included. Based on blood lead level (BLL), the cases were divided into 2 mild (BLL;40-69 µg/dL) and moderate (BLL;70-100) groups. Both groups received D-penicillamine (D-P) as a Chelator. Changes in BLL compared between two groups. All cases were oral opium users. Abdominal pain (75%), anorexia (55.6%), and constipation (53.2%) were the most common symptoms of lead poisoning. 67.8% of cases experienced only one round of chelation therapy and "Rebound phenomenon" happened in 9% of these. Ninety percent of the patients had wellbeing sensation, and symptoms improved at the end of the first round of treatment. The mean BLL before and after chelation therapy were 66.87 and 45.7 µg/dL, respectively. Oral Chelator reduced BLL in both mild and moderate poisoning groups (35.61% vs. 35.90%, *P*: 0.057), respectively. The comparison of BLL before and after chelation therapy showed that the treatment was effective equally in both mild and moderate toxicity. However, in a few cases, the rebound phenomenon may occur.

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Introduction

Lead is a widespread heavy metal which is toxic for human (1). Lead is known as a toxic material which affects different organ systems. Lead poisoning could be a result of occupational or environmental exposures, such as industrial emission, contaminated food, and soil. In addition, inhalation and ingestion of lead and dermal exposure to the lead compounds can cause lead poisoning (2). After exposure, the lead will be gathered in blood, soft-tissues, and bone, and cause numerous manifestations (3). Clinical symptoms of lead poisoning are non-specific and including abdominal pain, anorexia, constipation, anemia, muscular and skeletal pain, decreased libido, memory loss, and nephropathy (4).

Lead poisoning is diagnosed on the base of elevated blood lead levels (BLL). Termination of exposure to lead compounds is essential for treatment. Chelation therapy can be essential in lead poisoning which reduces the BLL promptly and help to recovery (5). Dimercaprol, calcium Na_2 EDTA, and Succimer are the agents mainly used for chelation therapy, and D-penicillamine is less frequently used. Chelation rapidly causes fall in BLLs after few days. It is suggested to recheck BLL one to three weeks after therapy, as lead levels may rebound due to the release of lead from storage sites (6,7). Treatment with a chelating agent can lower BLL; however, this may cause a "Rebound" phenomenon" by which lead levels rise in the blood since lead is released from the bones into the plasma (8).

Recent years, contaminated opium with lead also has been accepted as a new source of poisoning. In some studies, it was reported that lead toxicity happens as a result of drug use especially opium (9). Opium is contaminated by lead during its production process, or lead is deliberately added to opium to increase its weight or by growing in the contaminated soil (10-12). With regard to the high prevalence of opium dependency in Iran and also because of the complicated problems occur as a result of an increase in blood lead level, the present study evaluated the outbreak of lead poisoning in opium users and the efficacy of Chelation Therapy on BLL in

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opium users.

Materials and Methods

In this cross-sectional study, 133 opium users with a primary diagnosis of lead poisoning, who referred to Lead clinic of Firoozgar hospital from March 2016 to September 2017 were included. The study is approved by the ethical committee of Iran University of Medical Sciences and performed according to the Helsinki ethics principals. All participants were aware of the study, and written constant was obtained from them.

Inclusion and exclusion criteria

The inclusion criteria were using Opium with the presentation of lead poisoning and BLL more than 45 µg/dL. The exclusion criteria were severe poisoning (BLL more than 100, the presence of signs of encephalopathy), history of sensitivity to penicillin drugs or severe sensitivity during treatment like increase of liver enzyme more than 2-fold, and the presence of underlying liver or bone marrow diseases. Variables were including opium dosage, duration, and rout of usage, and symptoms and signs of toxicity. Diagnosis of lead poisoning was confirmed with an elevated blood lead level (BLL>25 µg/dL) by atomic absorption assay. Based on BLL, the cases were divided into 2 groups [one group with mild poisoning (BLL: 45-69 µg/dL) and another group with moderate poisoning (BLL: 70-100 µg/dL)]. In addition, RBC indices, kidney and liver function tests, the serum level of iron and ferritin were also measured.

The use of opium stopped, and all cases underwent standard detoxification with methadone. All cases also underwent at least one course of chelation therapy with D-penicillamine (D-P) 250 mg/qid for 10 days in an out-patient setting. BLL checked again five days after the end of therapy and that patient who still were symptomatic or/and had BLL over 25 µg/dL underwent second or third courses of D-P. The efficacy of D-P in lowering BLL compared in both groups. Finally, the response to chelation therapy with D-P was assessed by both decreasing in BLL and improvement of clinical symptoms and signs.

Statistical analysis

SPSS v20 was used to analysis the data. Qualitative data are presented as frequency and percent. The quantitative data are presented as mean±SD, and independent T-test was used to compare the results between the two groups. Values are significant at $P<0.05$.

Results

The mean age of cases was 48.54±12.31 years (Min; 20 and Max; 80). All patients were chronic oral opium abusers. The mean dose of opium was 2.70±1.67 g/day (Min; 0.5 and Max: 9). Out of 124 cases, 52 cases had moderate BLL (70-100 µg/dL), and 72 cases had a mild BLL level (BLL: 40-69 µg/dL). Table 1 shows the symptoms and signs of cases in two mild and moderate groups.

Table 1. The symptoms and signs of cases in two mild and moderate groups

Symptoms and signs	Blood Lead Level, µg/dL [No. (%)]			*P*
	Mild toxicity (40-69 µg/dL) n = 72	Moderate toxicity (70-100 µg/dL) n = 52	Total N = 124	
Abdominal pain	55 (76.4%)	38 (73.1%)	93 (75%)	0.674
Anorexia	39 (54.2%)	30 (57.7%)	69 (55.6%)	0.697
Constipation	40 (55.6%)	26 (50%)	66 (53.2%)	0.541
Nausea & vomiting	3 (4.2%)	6 (11.5%)	9 (7.3%)	0.118
Anemia	15 (20.8%)	8 (15.4%)	23 (18.5%)	0.441
Paresthesia	23 (31.9%)	15 (28.8%)	38 (30.6%)	0.712
Weight loss	1 (1.4%)	1 (1.9%)	2 (1.6%)	0.816
Lead gum	4 (5.6%)	3 (5.8%)	7 (5.6%)	0.959
Muscle weakness	19 (26.4%)	20 (38.5%)	39 (31.5%)	0.153
Muscles and/or joint pain	9 (8.2%)	5 (7.6%)	14 (11.3%)	0.084
Loss of memory	2 (2.8%)	2 (3.8%)	4 (3.2%)	0.740
Leg edema	5 (6.9%)	9 (17.3%)	14 (11.3%)	0.072

Abdominal pain (75%), anorexia (55.6%) and constipation (53.2%) were the most common symptoms of lead poisoning, respectively. 11.3% of patients suffered from swelling of the feet at the time of referral and before the treatment with a chelator. All of these patients had normal renal function and serum T4, TSH

and protein levels. Edema was not improved by treatment with a chelator, and there was persistent edema up to 2 months after treatment. Edema of organs caused by lead poisoning has not been reported in any previous article.

According to table 2, after the first round of chelation therapy, the BLL is reduced to the proper level in 67.8% of cases, and they didn't need more chelation therapy. However, 40 (32.2%) of cases needed two rounds of chelation therapy. In addition, 12% of cases had three rounds of chelation therapy. From these 40 cases, 10 cases were treated due to rebound phenomenon, and 30 cases were treated due to the presence of blood lead of more than 40, or some abdominal symptoms, anorexia and muscle aches. In the first round of chelation therapy from 124 cases, rebound phenomenon showed in 11 cases. From 40 cases who experienced two rounds of chelation therapy, a rebound phenomenon observed in 10 cases and among 15 cases who underwent three rounds of chelation therapy, a rebound phenomenon observed in 4 cases.

Table 2. The rounds of chelation therapy

Chelation therapy	Mild Toxicity (n = 72)	Moderate Toxicity (n = 52)	Total N=124
One round	54	30	84 (67.8%)
Two rounds	18	22	40 (32.2%)
Three rounds	5	10	15 (12%)

Table 3 shows that 54.8% of cases had more than 50% reduction in lead level which considered as moderate effectiveness of chelation therapy.

Table 3. The of chelation therapy in lowering the level of BLL

Chelation therapy effectiveness	No. (%)
Proper > 50% (50-70%)	20 (16.12%)
Moderate (25-50%)	68 (54.8%)
Low (10-25%)	26 (20.96%)
Very low (< 10%)	2 (x%)

With regards to the results, the mean BLL before and after chelation therapy were 66.87 and 45.7 µg/dL, respectively which shows that 10-day D-P can reduce BLL 35.74%. The comparison of BLL before and after chelation therapy in two groups of mild and moderate toxicity showed that the treatment was effective equally in both groups (35.61% vs. 35.90%, *P*: 0.057) and there was not a significant difference in BLL reduction that was consistent with clinical results which shows improvement 3 to 5 days after chelation therapy (Table 4).

According to the results, the level of Hemoglobin (10.9±2 vs. 12.77±1.41, *P*:0.000) and MCV (82.62±8.3 vs. 85.72±5.39, *P*:0.000) showed significant differences before and after the chelation therapy.

Table 4. The BLL level before and after the chelation therapy

	Mild toxicity	Moderate toxicity	Total
Before therapy (mean)	56.19	82.74	66.87
After chelation (mean)	40.40	53.04	45.70
Mean decrease in BLL (%)	35.61%	35.90%	35.74%

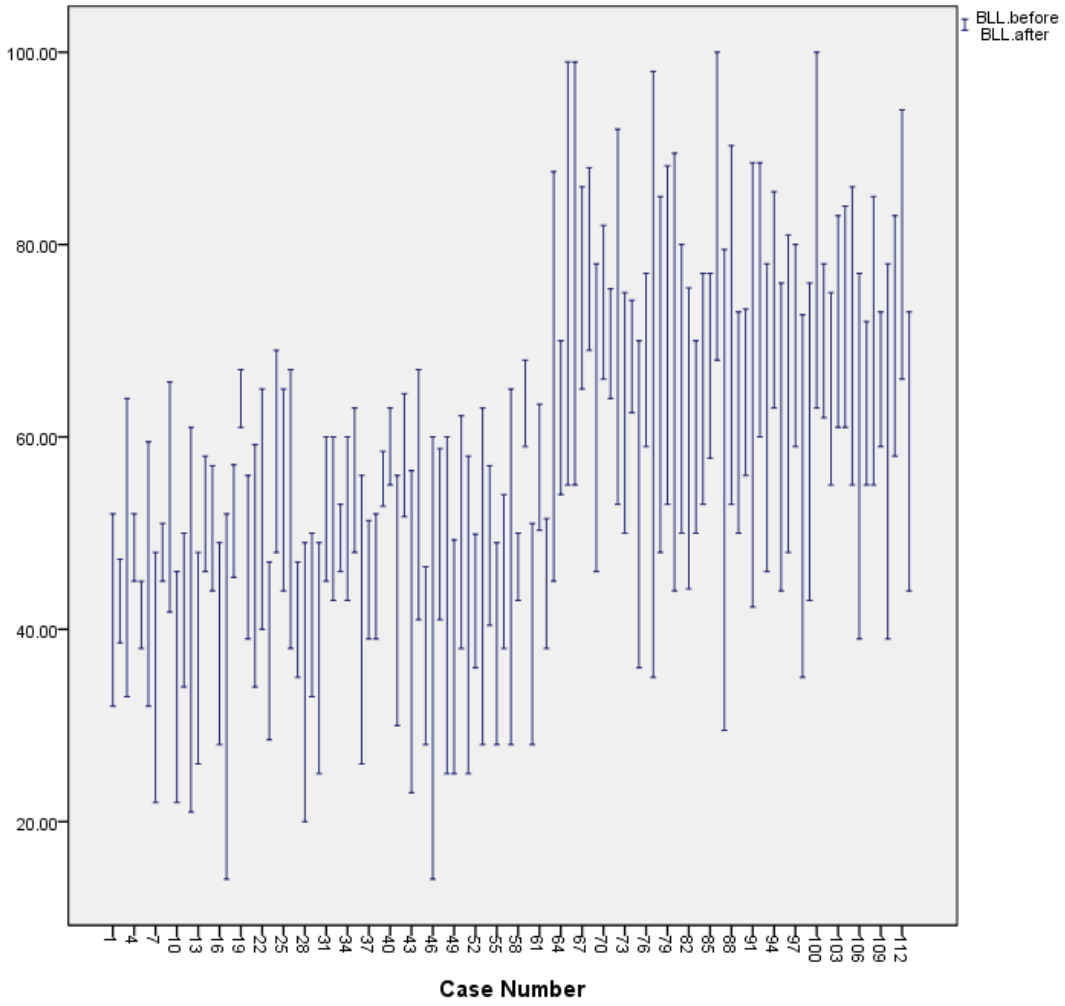

Figure 1. High/Low graph showing the range of BLL for each patient

Discussion

Opium is one of the important abused substances, and opium dependency is an important health issue in developing countries. In addition, opium is the most prevalent drug used in Iran (13). Lead poisoning in opium users currently is one of the main forms of non-occupational and non-industrial lead poisoning in Iran. In the present study, we evaluated the outbreak of lead poisoning in opium users and the efficacy of Chelation Therapy on BLL in opium users.

According to the result of the present study, the main manifestations of the lead poisoning in the opium users are including abdominal pain (75%), anorexia (55.6%) and constipation (53.2%). The result is consistent with the result of Aghaee Meybodi *et al.*, which showed that the main clinical presentations are anorexia (96%), abdominal pain (92%), muscle weakness (92%), constipation (88%), and pain in the extremities (88%), respectively (12). In another study by Afzali *et al.*, the main symptoms were constipation and abdominal pain (14).

The results of this study showed that the mean BLL in patients with mild toxicity was 56.19 µg/dL, in moderate toxicity was 82.74 µg/dL, and totally in patients with lead poisoning, it was 66.87 µg/dL. In Hayatbakhsh *et al.*, study the mean BLL in 249 opium users was 91.02±59.83 µg/dL (15). The mean BLL in Froutan *et al.*, the study was 51.17±27.96 µg/dL in 42 opium users (16). In Afazeli *et al.*, study the mean of BLL was 22.41±21.14 µg/dL in opium users and 4.02±3.16 µg/dL in non-users, and it was significantly higher in opium users (14). Amiri *et al.* showed that the mean BLL in 39 opium dependent individuals was 57.04±46.03 µg/dL and was 16.70±12.51 µg/dL in control group and it was significantly higher in opium users (P=0.045) (17). The higher BLL in opium users are due to contamination of opium with lead during its production process or because of deliberately adding

of lead to opium to increasing its weight (11,12).

The result of this study demonstrated that the chelation therapy, 10-day D-P could reduce BLL. The comparison of BLL before and after chelation therapy in two groups of mild and moderate toxicity showed that the treatment was effective equally in both groups. Also, improvement was seen in patients' clinical presentations 3 to 5 days after chelation therapy. Moreover, the effectiveness of chelation therapy was moderate (25-50%) in most of the cases in this study. After the first round of chelation therapy, the BLL is reduced to the proper level in 67.8% of cases, and they didn't need more chelation therapy. However, 32.2% of cases needed two rounds of chelation therapy and 12% of cases needed three rounds of chelation therapy. D-penicillamine that is used in this study is a reducing chelator. By decreasing lead cations, it reduces their binding affinity to proteins and entirely stimulates their secretion in urine (18). Iijimaa *et al*., in their study showed that in a patient with lead poisoning, administration of D-penicillamine raised the urinary lead excretion, resolved the abdominal pain, liver dysfunction, and anemia and the BLL remained normal after one year (19). In another study by Soon Duck Kim, the effects of oral D-Penicillamine in industrial lead poisoning treatment is evaluated, and it was demonstrated that the blood lead level, hemoglobin, and urine coproporphyrin and aminolevulinic acid reduced after one month and the clinical symptoms disappeared after two months (20). González-Ramírez *et al*., the study revealed that the administration of Penicillamine in patients who had occupational exposure for several years had a positive response. They evaluated the daily removal of urinary lead, delta-aminolevulinic acid and coproporphyrin. They assessed the hematic lead and protoporphyrin IX weekly. The results indicated that penicillamine can be an alternative to ethylene diamine tetraacetic acid (EDTA) in the chelatable lead mobilization test and verified that it is a good alternative in the treatment of chronic lead toxicity (21). Studies reported that chelation therapy is effective in lowering blood lead levels. However, it may not be successful in preventing from lead associated cognitive effects because they probably cannot remove enough amounts of lead from tissues (22,23). Apart from penicillamine which used in the current study, there are three other main chelators including dimercaprol, edetate calcium disodium (calcium EDTA), and succimer (22,24,25). Dimercaprol is the best chelator for encephalopathy treatment, or other severe signs of lead poisoning and its recommended dosage is 75 mg/m^2 i.m. every 4 hrs and for 5 days (24,25). Calcium EDTA is effective but may raise the distribution of lead into the CNS, and it is recommended to be used along with dimercaprol (22). The recommended dosage is 1000-1500 mg/m^2 per day. Succimer is the best chelator for mild lead poisoning, and the recommended dosage of it is 350 mg/m^2, 3 times a day and for 5 days (22).

The results showed that in the first round of chelation therapy from 124 cases, rebound phenomenon observed in 11 cases, from 40 cases that experienced two rounds of chelation therapy, rebound phenomenon observed in 10 cases and among 15 cases that underwent three rounds of chelation therapy, rebound phenomenon observed in 4 cases. During chelation therapy in some cases, lead levels may rise in the blood due to releasing of lead from the bones into the plasma which is called rebound phenomenon (8). In a study by Shannon and Townsend, 4 out of 55 children with mild to moderate lead poisoning showed an increase in the lead concentrations during treatment with D-penicillamine (26).

The oral use of opium contaminated with Lead can cause acute or chronic lead poisoning, and its most common clinical manifestation is acute and chronic abdominal pain with constipation and anemia. The diagnosis of lead poisoning is easy and, with suspicion of consumption of opium, the blood lead level should be measured. Patients should be detoxified and treated with a chelator. Oral administration of D-penicillamine is effective in decreasing the level of lead and improving symptoms in mild to moderate toxicity and there no serious complication was observed.

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