Research Paper: The Biochemical Outcome of Two Treatment Protocols in Patients With Opium-associated Lead Poisoning: A Cross-sectional Study in North of Iran

Alireza Badsar[1] , Zeynab Gholami[2] , Morteza Rahbar Taramsari[1] , Zahra Atrkar Roshan[3] , Hamid Mohammadi Kojidi[1], Monireh Aghajany-Nasab[2,4*]

1. Department of Forensic Medicine, School of Medicine, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran.
2. Anzali International Campus, Guilan University of Medical Sciences, Rasht, Iran.
3. Department of Statistic, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
4. Department of Biochemistry, Molecule and Cell Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.

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ABSTRACT

Background: Lead is a potent toxin that targets heme synthesis and some antioxidant enzymes that induce oxidative stress. Lead exposure remains one of the significant health concerns all over the world. Chelating agents have been used as antidotes for acute and chronic lead poisoning. The present study was conducted to evaluate the biochemical outcome of two different chelating therapies.

Methods: This descriptive cross-sectional study was performed in the Razi University Hospital, Rasht, Guilan. Fifty-six patients with a history of opium use were enrolled in the study who were treated symptomatically. Blood Lead Llevels (BLL), Hemoglobin (Hb), Red Blood Cell (RBC), White Blood Cell (WBC), urea, creatinine, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Alkaline Phosphatase (ALP) were evaluated before and after treatment. The BLL more than 100µg/dl with clinical symptoms was considered as severe lead poisoning (n=34) who received 4 days of DMPS (2,3-dimercaptopropane-1-sulfonate) injection. Other cases with BLL of 20-100µg/dl were considered as those with mild poisoning (n=22) that were treated with oral D-Penicillamine for 14 days.

Results: The mean age of patients was 49.73±14.11 years. Data analysis indicated no significant differences between the groups at baseline regarding the demographic variables. A significant reduction was observed in BLL before and after the intervention using the D-Penicillamine from 75.88±26.22 to 44.3±17.51 µg/dl (P=0.0001). The BLL reduced from 105.5±34.04 to 24.51±24.08 µg/dl after treatment with DMSP (P=0.0001). The levels of ALT, AST, and WBC significantly decreased post-treatment following using D-penicillamine and DMPS (P<0.05). The D-Penicillamine-treated group showed an increase in Hb and RBC (P<0.05).

Conclusion: According to the results, penicillamine improves low to moderate lead toxicity. Although DMSP decreases BLL significantly and reverses liver enzymes, further investigations on Hb and RBC, are needed.

* **Corresponding Author:**
Monireh Aghajany-Nasab
Address: *Department of Biochemistry, Molecule and Cell Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.*
Tel: *+98 (911) 3810964*
E-mail: *maghajany@gmail.com*

1. Introduction

Lead Poisoning (LP) is a growing risk for public health. The lead exposure may affect industrial and mining workers, and painters. Lead is found in water and air pollution and cosmetic products. In black markets, some materials, like heavy metals, especially lead are added to opium products to increase the weight to earn more money [1]. Opium abusers may be at the risk of LP. Some factors, such as age, individual health, and nutritional status are essential in the absorption and biological fate of lead. It can affect hematopoietic, renal, neurological, gastrointestinal, and cardiovascular systems [2].

Lead can mainly reach the lower respiratory tract via inhalation and enters the bloodstream and is excreted in urine through glomerular secretion and tubular filtration. A small part of the ingested lead is absorbed in the gastrointestinal tract, which is excreted through feces. Lead is generally bound to Red Blood Cells (RBCs) and the remaining part is attached to plasma proteins. The amount of absorption and excretion should be in equilibrium; otherwise, it will pass the internal organs, especially bone marrow, liver, brain, and kidney. The lead biological half-life is from 1 month to 20 years [3]. It can develop anemia, nausea, vomiting, constipation, abdominal pain, and tenderness, icterus, hypertension, headache, dizziness, seizure, coma, and neuropathy [4].

Blood lead assessment is the first diagnostic test for LP, which may be done in biochemical labs. In all suspected LP cases, an elevation in liver enzymes, kidney function test, and anemia are the other features that should be assessed. These patients are mostly misdiagnosed as acute abdomen, chronic pancreatitis, hospitalized, and sometimes undergo unnecessary surgeries. Chelation therapy has long been used as the main treatment for LP to remove the lead from various organs and pass it through the urine [2].

An ideal chelator should have high water solubility, greater affinity to lead, and lower toxicity than lead. The ability to penetrate cell membranes and rapid elimination via forming non-toxic complex should be considered for successful chelating therapy for all metal toxicities. Ethylene Diamine-Tetra Acetic acid (EDTA), British Anti-Lewisite or dimercaprol (BAL), D-penicillamine, and 2, 3-Dimercaptoduccinic Acid or succimer (DMSA) are used as chelators in the clinics [5]. In the United States, DMSA and CaNa2EDTA (calcium edentate or calcium disodium versenate) are the first- and second-line treatments, and D-Penicillamine is the third-line treatment, while in Europe, it is the first-line therapy [6].

Many patients treated with BAL develop side effects, like sweating, fever, hypertension, headache, nausea, vomiting, and palpitations [7]. Two types of EDTA (Na2EDTA and CaNa2EDTA) salt are used in medical practice. The side effect of Na2EDTA is electrolyte imbalance. Serious complications and deaths have also been reported regarding Na2EDTA; therefore, it has been replaced with other drugs nowadays [8]. D-penicillamine is a reducing agent that has been used for several decades to treat poisoning with heavy metals, including lead [9]. However, due to numerous reports of life-threatening reactions, such as renal and bone marrow disorder (leukopenia and thrombocytopenia) and skin complications, it is used as the third-line of treatment [10-12]. DMPS is also a chelator that is commonly used to treat poisoning with heavy metals. This drug is a water-soluble analogue of BAL that produces fewer complications [13]. DMPS may induce complications, such as digestive discomfort, skin reactions, mild neutropenia, and elevated liver enzymes, but the prevalence of these complications is not significant [14].

Regarding the Iranian guideline for chelation therapy in LP, the BAL and CaNA2EDTA are proposed as the first-line therapy for encephalopathy and blood lead levels greater than 100 µg/dl. If these two drugs are not available, oral DMSA could be used, and finally, D-penicillamine should be administrated. For blood lead levels of 70-100 µg/dl, the first-line therapy is DMSA, and the second-line could be D-penicillamine [3].

All chelators have some complications, and their administration is based on the patient's condition. An ideal chelator should increase the release of lead and should be available and safe [15]. The use of the best chelator has always been considered by physicians, and several studies have been conducted to evaluate and compare their therapeutic effects [16, 17]. Due to the different characteristics of these drugs, such as their different costs and complications, it is essential to evaluate the response to existing drugs so that the results can help physicians to select the appropriate drug according to the condition. The best approaches and management in lead toxicity may be achieved only after performing reliable diagnostic lab tests.

As LP among Iranian opium abusers has been reported in several studies [18-20], the aim of this study was to evaluate the biochemical outcome of two different chelating therapies.

2. Materials and Method

All patients in this cross-sectional study had severe and debilitating symptoms (digestive, renal, and nervous symptoms) with a history of opium abuse suspected of LP. The admitted patients to the Razi University Hospital as a referral center of poisoned patients in the north of Iran from February 2016 to January 2017, which had a complaint of abdominal cramps were enrolled in the study. The appropriate sample size was determined by comparing the means formula and derived from a pilot study with a 95% confidence level and 90% power.

The exclusion criteria were hepatitis and dialysis patients, pregnant and lactating women, and the patients with previous complications with chelating agents. Patients' data were gathered using data collection forms.

The patients' physical examination, blood lead levels, serum Hemoglobin (Hb), RBC, liver, and kidney function tests were evaluated at the time of admission, and all patients were treated symptomatically. All biochemical and hematological parameters were evaluated before and after the treatment. The blood lead level was determined by Perkin Elmer (Norwalk, CT, USA) spectrometer and Flame Atomic Absorption Spectrometry (FAAS) equipped with an autosampler.

Serum urea concentration was quantified using the Berthelot Enzymatic and photometric method (Pars Azmoon Co., Tehran, Iran). Serum creatinine was measured by Jaffe's method. Creatinine forms an amber yellow complex with alkaline picrate (picric acid + 0.75 N NaOH), which is measured photometrically (Pars Azmoon Co., Tehran, Iran). Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) were determined with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) approved Procedures for the measurement of catalytic activity of enzymes using Pars Azmoon Photometric kits. The study was approved by the Ethics Committee of Guilan University of Medical Sciences.

Treatment protocols

The chelating agents used in the present study were Dimaval (DMPS) and D-penicillamine and were used based on availability and guidelines of the Iranian Ministry of Health. Patients whose clinical symptoms persisted or became severe, those with blood lead levels of more than 100 µg/dl, or cases who had encephalopathy, were treated with DMPS 250 mg intravenous injection three times a day for about four days. Patients with a blood lead level of 70-100 µg /dl or patients with a blood lead level of 20-70 µg/dl with mild poisoning symptoms were treated with oral D-penicillamine (250 mg) four times a day for 14 days. Patients with normal blood lead levels or those with drug allergies were excluded from the study. After the treatment period, 14 days after treatment with D-penicillamine, and four days after treatment with DMPS, blood lead levels and other laboratory tests were re-evaluated.

Statistical analysis

Descriptive statistics were used to describe the data. The mean, Standard Deviation (SD), and range of quantitative variables were calculated. The Chi-square and Fisher's exact tests were performed to assess demographic characteristics. A one-sample Kolmogorov-Smirnov test was used to evaluate the normal distribution for quantitative data. Regarding data with normal distribution, t-test and paired t-test were used. The mean values of each laboratory test before treatment in the two groups were compared using a t-test. The Independent-samples t-test or student's t-test was used to determine whether there is a statistically significant difference between the means in the two groups. Within-group differences were assessed using paired t-test. All tests were two-sided and a $P<0.05$ was considered significant. Levene's test was done to test homogeneity of variances. A one-way ANCOVA was conducted to analyze the data by the SPSS version 16.0. (IBM, Chicago, IL, USA) software.

3. Results

Of 56 patients, 92.9% were male and 7.1% were female. Most patients aged 24-72 years with a Mean±SD age of 49.73±14.11% years and 73.2% were more than 40 years old. Also, 34 patients (60.7%) were treated with DMPS and 22 patients (39.3%) were treated with D-penicillamine. The Mean±SD age of the patients in each group was 51.05±14.62 and 47.68±13.35 years, respectively. No significant difference was found in the patients' age, gender, occupation, and education between the two groups ($P>0.05$; Table 1).

The blood lead level and activity of liver enzymes, including ALT and AST significantly decreased after four days of DMSP administration ($P=0.0001$, $P=0.008$, and $P=0.026$, respectively; Table 2). However, the effect of DMPS on the other biochemical tests, including Hb, Blood Urea Nitrogen (BUN), and creatinine were not statistically significant between the two groups ($P>0.05$; Table 3). The activity of ALT and AST significantly decreased after 14 days of treatment with D-penicillamine

Table 1. Demographic characteristics of the patients with lead poisoning in the groups treated by DMPS and D-penicillamine

Variables		No. (%)			P
		Treated with DMPS (n=34)	Treated with D-Penicillamine (n=22)	Total (n=56)	
Age (y)	<40	8 (23.5)	7 (31.8)	15 (26.8)	0.86*
	41-50	11 (32.4)	7 (31.8)	18 (32.1)	
	51-60	6 (17.6)	4 (18.2)	10 (17.9)	
	<60	9 (26.5)	4 (18.2)	13 (23.2)	
Gender	Male	32 (94.1)	20 (90.9)	52 (92.9)	0.642**
	Female	2 (5.9)	2 (9.1)	4 (7.1)	
Occupation	Unemployed	13 (38.2)	5 (22.7)	18 (32.1)	0.108*
	Farmer	4 (11.8)	0 (0)	4 (7.1)	
	manual Worker	9 (26.5)	5 (22.7)	14 (25)	
	Employed	4 (11.8)	4 (18.2)	8 (14.3)	
	Self-employed	4 (11.8)	8 (36.4)	12 (21.4)	
Education	Under Diploma	19 (55.9)	8 (36.4)	27 (48.2)	0.36*
	Diploma	12 (35.3)	11 (50)	23 (41.1)	
	Bachelor and Higher	3 (8.8)	3 (13.the 6)	6 (10.7)	

*Using Chi-Square test; **Using Fisher's exact test

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(P=0.029, and P=0.003, respectively), while the Hb level in the patients of this group significantly increased (P=0.025). The BUN and creatinine were more than normal ranges only in 12%and 14% (respectively) of the patients in both groups. The student's t-test showed a statistically significant difference between the lead means in the two groups (P=0.007, Table 2).

Table 4 indicates that the F-value for ALT was 0.170 and it was not significant (P=0.682). The pre-treatment value of ALT in the DMPS and penicillamine groups did not cause a significant effect on patients post-treatment of ALT in DMPS and penicillamine groups. The pre-treatment values of RBC, WBC, ALT, AST, BUN, and creatinine showed no significant difference with the patient's post-treatment values in both groups using one-way ANCOVA (P>0.05).

4. Discussion

This study was conducted in order to assess biochemical outcomes of two different chelation therapies for the treatment of opium-associated LP patients. The results of the present study confirmed that the blood lead level was higher in some opium abusers, which significantly decreased after the injection of DMPS (Figure 1). This result is consistent with the results of the Blaurock and Busch study. They concluded venous DMPS was the most appropriate chelator for the treatment of those exposed to one or more metals, including lead, antimony, arsenic, and mercury [13].

D-penicillamine administration for 14 days could significantly decrease the blood lead level in this study. Similar results were reported by Porru and Alessio, who revealed a significant decrease in the lead level in patients [22]. Oral penicillamine in cross combination with intravenous DMPS was evaluated by Xu et al.. They confirmed that the clinical efficacy and safety of chelation treatment with this combination can relieve symptoms of metal toxicity [23].

Heavy metals toxicity is considered a health-threatening problem and needs attention in some cases. LP attracts great attention because of causing environmental pollution and occupational poisoning, also regarding

Table 2. Lead changes before and after chelation therapy in patients with opium-associated lead poisoning

Variable	Mean±SD								
	DMPS			D-Penicillamine			Differences Between Two Groups		
	Before	After	P	Before	After	P	DMPS	Penicillamine	P
Lead (µg/dl)	105.5±34.04	51.24±24.08	0.0001*	75.3±26.22	44.03±17.51	0.0001*	-54.33± 32.33	-31.35±25.89	0.007**

*Paired t-test.

**Independent t-test.

Table 3. Laboratory test changes before and after chelator administration in patients with lead poisoning in the groups treated by DMPS and D-penicillamine

Variables	Mean±SD			
	Before Treatment		After Treatment	
	DMPS	D-Penicillamine	DMPS	D-Penicillamine
Hb (mg/dl)	9.08±1.86	10.68±2.1[a]	9.51±1.95	11.38±1.9[b,d]
BUN (mg/dl)	15.91±5.1	16.26±6.36	17.88±14.13	13.82±3.73[d]
Cr (mg/dl)	1.01±0.17	0.99±0.21	0.99±0.22	0.93±0.15
ALT(U/L)	45.52±37.2	59.1±57.5	32.23±23.4[c]	33.9±20.3[d]
AST(U/L)	40.44±22.5	47.59±28.9	31.8±15[c]	33±15.36[d]
WBC	8.8±3.7	8.5±1.9	7.3±2.4[c]	6.9±1.2[d]
RBC	3.4±0.7	3.9±0.6[a]	3.6±0.9	4.04±0.6 [b,d]

[a]Significant differences between the two groups before treatment (P<0.005).

[b]Significant differences between the two groups after treatment (P<0.005).

[c] Significant differences before and after treatment within the DMSP group (P<0.005).

[d] Significant differences before and after treatment within the D-Penicillamine group (P<0.005).

opium abusers. The lead-poisoned patients who refer to health care services with severe abdominal pain, are subjected to routine biochemical and hematological laboratory tests, and almost always without blood lead assessment, they are asked to perform an abdominal x-ray and/or a CT scan. It has been documented that unnecessary surgical intervention may be considered for some misdiagnosed cases [21]. Although LP needs early diagnosis to perform an appropriate intervention, the blood lead assessment sometimes may be ignored. The best chelating agents must be selected as soon as the lead blood levels are more than 40 µg/dL (normal values: less than 10 µg/dL).

In the present study, there was a significant difference between the amount of ALT and AST before and after the intervention using DMPS, which is consistent with other studies. Xu et al. reported that DMPS was associated with improved hepatic function in 71% of lead-induced poisoning patients over the follow-up period of 6 months to 5 years; ALT significantly decreased after treatment with DMPS [23]. Cao et al. in 2015 found that DMPS could significantly reduce liver enzymes, which is consistent with the results of the present study [24]. We found significant differences between the levels of ALT and AST before and after treatment with D-Penicillamine. Jalali et al. reported that D-penicillamine administration in lead-induced liver toxicity and oxidative stress could significantly lower ALP, ALT, and AST and improve liver antioxidant enzymes [15] Shadfar in 2019 reported that liver enzymes reduced after chelating therapy by D-penicillamine [16]. A similar outcome was also proved by Schroder et al. in 2015 in the United States [25].

Table 4. One-way Analysis of Covariance (ANCOVA) for assessing between subject effects dependent variable: ALT after treatment

Sources	Sum of Squares	df	Mean Square	F	Sig.	Partial Eta-squared
Intercept	8111.561	1	8111.561	23.937	0.000	0.311
ALT before treatment	8875.823	1	8875.823	26.192	0.000	0.331
Group	57.682	1	57.682	0.170	0.682	0.003
Error	17960.113	53	338.87			

D-penicillamine is a chelator that is metabolized in the liver and eventually is excreted through the kidneys and feces [22]. As the kidney is one of the main target organs associated with lead toxicity, renal function was evaluated in the present study. The creatinine and BUN levels of only about 12-14% (respectively) of patients were more than normal ranges. Lead nephrotoxicity was not observed in this study. Other lead toxicity symptoms, such as abdominal pain and anemia are more reported in opium-associated LP. Porru et al. found that the reduction in the level of creatinine and BUN after administration of D-penicillamine was not statistically significant [22]. Xu et al. in 2013 showed that after administration of intravenous DMPS, serum level of creatinine and 24-hour BUN levels were higher compared with using oral D-penicillamine [23]. Also, in another study conducted by Cao et al. in Norway in 2015, DMPS was introduced as a relatively new drug that could release lead and mercury deposits in the urine. This drug has relatively small toxicity compared with the classical antiemetic BAL [24]. Considering the mentioned DMPS renal elimination mechanism, it may cause a slight increase in BUN after taking DMPS. Other factors, such as high levels of lead in this group of patients can also be effective. Chemical chelators, such as D-penicillamine and DMPS have long been used in the treatment of LP, resulting in a significant reduction in lead levels, and they can decrease the mortality rate caused due to poisoning with heavy metals, such as lead and copper [26]. The kidney and neurological complications associated with the use of these chelators have not been addressed yet, which requires further research in this regard.

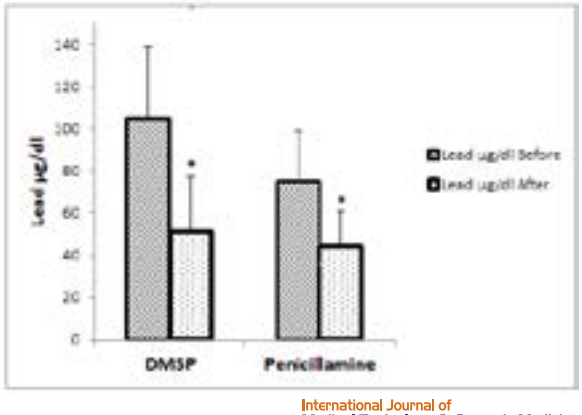

Figure 1. Lead levels (µg/dl) before and after Treatment with DMSP and Penicillamine

LP should be considered as one of the primary differential diagnoses in patients with gastrointestinal symptoms with a positive history of opium abuse [27]; thus, assessment of blood lead levels and biochemical markers are necessary. These patients need to receive suitable chelating therapy and should be followed up to prevent acute symptoms.

Some patients did not cooperate in post-treatment tests after improving the symptoms, which was one of the limitations of our study. The cross-sectional design, relatively small sample size, and inclusion of only males were other limitations of this study Conducting cohort studies can indicate the chronic adverse effects of these chelating agents in LP.

5. Conclusion

The biochemical parameters can be improved by careful medical supervision in LP. Blood lead level and the liver and kidney function test may be appropriate markers for evaluating chelating agents' efficacy in lead-induced damages. Penicillamine improved low to moderate lead toxicity and decreased biochemical scores compared with the pre-treatment stage. Although DMSP decreases blood lead level significantly and reverses liver enzyme properly, further investigations are needed to consider Hb and RBC. According to the results, kidney function may not necessarily be affected by opium-associated LP while blood lead level and liver enzymes could be considered as markers in chelation therapy.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Guilan University of Medical Sciences (IR.GUMS.REC.1396.386).

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Author's contributions

All authors equally contributed in preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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