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ORIGINAL ARTICLE

Retrospective Evaluation of Liver and Kidney Functions in Patients with Chronic Occupational Lead Intoxication Treated with EDTA Chelation Therapy*

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ABSTRACT

Objective: This study aimed to investigate hepatic and renal functions in patients who received calcium disodium edetate ($CaNa_2EDTA$) chelation treatment for chronic occupational lead intoxication.

Material and Methods: This single-center retrospective descriptive research was conducted in a secondary-level health facility. The study included patients treated with $CaNa_2EDTA$ chelation for chronic occupational lead intoxication between September 15, 2020, and May 31, 2021. Demographic and occupational characteristics, as well as and laboratory parameters obtained before and after the chelation therapy were evaluated.

Results: All 75 patients were male, and 73.3% had an occupation in metal scrap recycling. Renal parameters were within normal range before and after the chelation. However, mild elevations were observed in liver parameters. After the adjustment for demographic and occupational variables, the odds of having an elevated liver parameter and an elevated alanine transaminase (ALT) result after the chelation therapy were 9.3 (95%CI 2.6–33.2, p<0.001) and 11.4 (95%CI 2.4–53.2, p<0.001) for patients with pre-chelation elevated any liver parameter and pre-chelation elevated ALT result, respectively.

Conclusion: The current study documented mild elevations of the liver parameters in patients with chronic occupational lead poisoning after $CaNa_2EDTA$ chelation therapy, particularly those with elevated basal liver parameters, although their renal parameters stayed within reference ranges. The results serve as an example of the safe application of $CaNa_2EDTA$ chelation for chronic occupational lead poisoning, by monitoring kidney and liver parameters in a secondary-level health facility. Future prospective studies with structured treatment protocols may investigate the risk and determinants of hepatic and renal adverse effects.

Keywords: occupational disease, lead poisoning, chelation therapy, edetic acid.

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* The preliminary results of this study were presented as an oral presentation at the 3rd International Industrial and Environmental Toxicology Congress, which was held between November 4-10, 2021, as a virtual congress.

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Received: 24 December 2022, Accepted: 28 February 2023, Published online: 31 March 2023

INTRODUCTION

Lead (element symbol, Pb) is a heavy metal with an atomic number of 82. Lead has been used since ancient times and is one of the most toxic environmental pollutants [1]. One of the primary causes of lead exposure to humans has been occupational. The exposure may occur in a wide range of work activities, including mining and extraction of the lead from ores, as well as manufacturing processes using lead alloys (e.g., batteries and plumbing components) or lead compounds (e.g., painting pigments), and recovery from lead-containing material or scrap [2].

The biological effects of lead on human health are diverse. Lethal effects are observed upon acute high-dose intoxication, but lead may also chronically affect central and peripheral nervous, cardiovascular, hematological, musculoskeletal, urinary, hepatic, gastrointestinal, and reproductive systems, according to exposure level [3]. Although the primary approach should be the prevention of exposure by health and safety measures applied according to a hierarchy of controls [4], chelation treatment of acute or chronic lead intoxication may be required [5]. The purpose of chelation therapy is to bind to the toxic metal, thereby capturing it in a less toxic substance form, for subsequent excretion [6]. An ideal chelator is defined as having a greater affinity with the metal and providing rapid elimination, as well as showing only low-level side effects [7].

Calcium disodium edetate ($CaNa_2EDTA$) has been one of the agents used in chelation treatment for lead poisoning since the 1950s [8]. It can be applied either through the intramuscular or intravenous routes, but it is usually advisable to monitor its application with biochemical tests during the course of treatment due to possible side effects [9]. The situation may become more complex, as chronic lead intoxication may result in the deterioration of kidney and liver functions [10]. However, data on renal and hepatic functions in Turkish patients with chronic lead poisoning treated with $CaNa_2EDTA$ are scarce. Therefore, this study aimed to evaluate hepatic and renal functions in patients who received $CaNa_2EDTA$ chelation treatment for chronic occupational lead intoxication.

MATERIALS AND METHODS

Study design, subjects, variables

This single-center retrospective descriptive study was conducted in a secondary-level health facility, namely Ankara Occupational and Environmental Diseases Hospital, located in Ankara, Turkey. The inclusion criterion was a positive history of treatment with $CaNa_2EDTA$ chelation for chronic occupational lead intoxication in Ankara Occupational and Environmental Diseases Hospital between September 15, 2020, and May 31, 2021. Exclusion criteria were missing pre- or post-chelation data, and unplanned treatment interruption due to the patient's demand.

The hospital's scheme for $CaNa_2EDTA$ chelation treatment included cycles of intravenous infusions for a daily dose of 30–50 mg per kilogram of body weight for five days, and one or two days of break in between, if subsequent cycles were needed. The daily dose was given in two infusions, each lasting approximately 4 hours. The scheme also included laboratory monitoring, i.e., biochemical tests and blood lead levels, on the third day and at the end of the cycle, to decide whether treatment should be continued or finished.

The collected data were age, sex, body weight (in kg), height (in cm), body mass index (in kg/m2), duration of exposure, number of chelation treatment cycles, serum levels of alanine transaminase (ALT, in U/L), aspartate transaminase (AST, in U/L), gamma-glutamyl transferase (GGT, in U/L), direct and total bilirubin (in mg/dL), creatinine (in mg/dL), blood urea nitrogen (BUN, in mg/dL), and blood lead levels (in mg/dL) both before and after the chelation. Elevated values for creatinine, BUN, ALT, AST, GGT, and direct and total bilirubin were determined based on laboratory reference values.

Statistical analysis

Descriptive statistics are shown as numbers and percentages for categorical variables. The normality of the continuous variables was analyzed using the Shapiro–Wilk test, and means with standard deviation (SD), or medians with interquartile range (IQR) values were given accordingly. The pre- and post-chelation laboratory parameters of patients were compared using the paired samples t-test or Wilcoxon signed-rank test for continuous variables.

The pre- and post-chelation liver parameters were also compared as normal versus elevated, using the McNemar test. The significant associations between elevated results pre- and post-chelation were analyzed using logistic regression models with adjustment for age, BMI, lead blood level pre-chelation, duration of exposure, and the number of treatment cycles. The odds ratio (OR) values together with 95% confidence interval (95%CI) were calculated. Type 1 alpha was accepted as 0.05 for all analyses, which were performed using IBM SPSS for Windows v.22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The study included data from 75 male patients. The demographic, occupational, and treatment characteristics of patients are shown in Table 1. The median values were 31 years (IQR 25–39) for age, and 24.7 kg/m2 (IQR 22.7–29.0) for BMI. Eighty percent of subjects were current smokers, and an additional 6.7% were ex-smokers. There were no patients with pre-existing kidney disease. There was one patient with hepatitis B surface antigen positivity. The median duration of occupational lead exposure was 24 months (IQR 7–36). The most common occupation among patients was metal scrap recycling (73.3%), followed by battery production, foundry, lead extraction from ores, and arms industry. The chelation therapy was completed in all patients by achieving treatment goals.

The comparison of laboratory results pre- and post-chelation, shown in Table 2, depicted a statistically significant difference in blood lead level, creatinine, BUN, ALT, GGT, and total and direct bilirubin. The pre- and post-chelation median values were 59.1 µg/dL (IQR 45.3–68.0) vs 19.1 µg/dL (IQR 15.3–24.5) for blood lead level (p<0.001), 13 mg/dL (IQR 11–16) vs 10 mg/dL (IQR 9–12) for BUN (p<0.001), 23 U/L (IQR 18–28) vs 24 U/L (IQR 17–33) for ALT (p=0.001), 21 U/L (IQR 14–29) vs 27 U/L (IQR 18–51) for GGT (p<0.001), 0.11 mg/dL (IQR 0.08–0.13) vs 0.10 mg/dL (IQR 0.07–0.12) for direct bilirubin (p=0.001), and 0.60 mg/dL (IQR 0.47–0.78) vs 0.50 mg/dL (IQR 0.38–0.65) for total bilirubin (p<0.001). The mean creatinine values were 0.74 mg/dL (SD=0.11) before the treatment and 0.77 mg/dL (SD=0.10) after the chelation (p=0.002).

Table 1. Demographic, occupational, and treatment characteristics

Characteristic	Value
Age, year, median (IQR)	31 (25-39)
Height, cm, median (IQR)	175 (170-180)
Weight, kg, mean (SD)	78.9 (14.5)
BMI, kg/m^2, median (IQR)	24.7 (22.7-29.0)
Smoking status, n (%)	
Never smoker	10 (13.3)
Ex-smoker	5 (6.7)
Current smoker	60 (80.0)
Duration of exposure, month, median (IQR)	24 (7-36)
Occupation, n (%)	
Metal scrap recycling	55 (73.3)
Battery production	7 (9.3)
Foundry	6 (8.0)
Lead extraction from ores	4 (5.3)
Arms industry	3 (4.0)
Number of chelation therapy cycles, median (IQR)	2 (1-3)

BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Table 3 demonstrates the comparison between pre- and post-chelation liver parameters, including ALT, AST, GGT, and total and direct bilirubin, regarding laboratory reference values. Twenty-three (30.7%) patients had at least one elevated parameter before chelation, but 33 (44.0%) had at least one elevated parameter after chelation (p=0.041). The number of patients with elevated liver levels was 15 (20.0%) for ALT, 4 (5.3%) for AST, 10 (13.3%) for GGT, 2 (2.7%) for direct bilirubin, and 4 (5.3%) for total bilirubin before chelation. After chelation, the number of patients with elevated liver levels was 27 (36.0%) for ALT, 10 (13.3%) for AST, 15 (20%) for GGT, 2 (2.7%) for direct bilirubin, and 2 (2.7%) for total bilirubin. There was a statistically significant difference between the percentages of patients with elevated ALT levels (p=0.008) pre- and post-chelation. Regarding the case with hepatitis B surface antigen positivity, the patient did not show any elevated results before or after chelation therapy. Although a higher median creatinine but a lower median BUN were observed after the chelation, there were no patients with levels above reference ranges for both parameters pre- or post-chelation.

The relationship between any liver parameter elevated post-chelation and elevated ALT levels with elevated results pre-chelation was evaluated with logistic regression analyses (Table 4). After the adjustment for age, BMI, lead blood level pre-

chelation, duration of exposure, and the number of treatment cycles, elevations in any liver parameter and ALT after the chelation were related to any liver parameter (adjusted OR [aOR]=9.3, 95%CI 2.6–33.2, p<0.001) and ALT level (aOR=11.4, 95%CI 2.4–53.2, p<0.001) elevated pre-chelation, respectively.

Table 2. Comparison of pre-and post-chelation laboratory parameters

Characteristic	Pre-chelation	Post-chelation	p-value
Blood lead level, µg/dL, median (IQR)	59.1 (45.3-68.0)	19.1 (15.3-24.5)	**<0.001***
Creatinine, mg/dL, mean (SD)	0.74 (0.11)	0.77 (0.10)	**0.002†**
BUN, mg/dL, median (IQR)	13 (11-16)	10 (9-12)	**<0.001***
ALT, U/L, median (IQR)	23 (18-28)	24 (17-33)	**0.001***
AST, U/L, median (IQR)	26 (15-36)	35 (20-54)	0.267*
GGT, U/L, median (IQR)	21 (14-29)	27 (18-51)	**<0.001***
Total bilirubin, mg/dL, median (IQR)	0.60 (0.47-0.78)	0.50 (0.38-0.65)	**<0.001***
Direct bilirubin, mg/dL, median (IQR)	0.11 (0.08-0.13)	0.10 (0.07-0.12)	**0.001***

Bold p-values indicate statistical significance. ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; GGT, gamma-glutamyl transferase; IQR, interquartile range; SD, standard deviation.

*Wilcoxon signed-rank test

†Paired samples t-test

Table 3. Comparison of pre-and post-chelation liver parameters according to elevation status

Pre-chelation measurement	Post-chelation measurement		p-value*
	Normal	Elevated	
Any liver parameter, n (%)			**0.041**
Normal	37 (71.2)	15 (28.8)	
Elevated	5 (21.7)	18 (78.3)	
ALT, n (%)			**0.008**
Normal	45 (75.0)	15 (25.0)	
Elevated	3 (20.0)	12 (80.0)	
AST, n (%)			0.146
Normal	62 (87.3)	9 (12.7)	
Elevated	3 (75.0)	1 (25.0)	
GGT, n (%)			0.125
Normal	59 (90.8)	6 (9.2)	
Elevated	1 (10.0)	9 (90.0)	
Total bilirubin, n (%)			0.625
Normal	70 (98.6)	1 (1.4)	
Elevated	3 (75.0)	1 (25.0)	
Direct bilirubin, n (%)			1.000
Normal	72 (98.6)	1 (1.4)	
Elevated	1 (50.0)	1 (50.0)	

Bold p-values indicate statistical significance. ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase.

*Mcnemar test

Table 4. Logistic regression analysis of post-chelation elevation in liver parameters

Parameter	Crude		Adjusted*	
	OR (95% CI)	p-value	aOR (95% CI)	p-value
Post-chelation elevated any liver parameter				
Pre-chelation elevated any liver parameter	8.9 (2.8-28.3)	**<0.001**	9.3 (2.6-33.2)	**<0.001**
Post-chelation elevated ALT				
Pre-chelation elevated ALT	12.0 (3.0-48.4)	**<0.001**	11.4 (2.4-53.2)	**<0.001**

Bold p-values indicate statistical significance. ALT, alanine transaminase; aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

*Adjusted with age, body mass index, pre-chelation blood lead level, duration of exposure, and number of treatment cycles

DISCUSSION

This study evaluated hepatic and renal functions of 75 Turkish patients treated with $CaNa_2EDTA$ chelation for chronic occupational lead poisoning. Their main occupation was metal scrap recycling (73.3% of patients). A statistically significant difference was detected in lead blood level, creatinine, BUN, ALT, GGT, and total and direct bilirubin obtained before and after the treatment. Although renal parameters were within normal range before and after the chelation, mild elevations were observed in liver parameters. The odds of having an elevated liver parameter and elevated ALT after the chelation therapy were 9.3 and 11.4, for patients with any liver parameter elevated pre-chelation and ALT elevated pre-chelation, respectively, after adjustment for age, BMI, lead blood level pre-chelation, duration of exposure, and the number of treatment cycles.

The findings demonstrated that the most common occupation among patients was metal scrap recycling. A review on lead exposure in developing countries with low or middle income defined various high-exposure work activities, including the manufacture of wares, jewelry, and decorative items (due to production and application of lead-containing glazes), battery production, demolition, welding, automobile radiator repair, and electronic waste recycling [11]. Koh et al. evaluated articles published between 1940 and 2010 in the United States, and found that most measurements were sourced from lead-based painting, joining, or cutting metals by heat, metal manufacturing, and battery production [12]. With regard to the situation in Turkey, a previous study from our hospital also demonstrated that most of the patients with lead exposure worked at a recycling facility [13]. Kuman-Oyman et al. evaluated patients diagnosed with lead intoxication in the Istanbul Occupational Diseases Hospital (Istanbul, Turkey) between 2012 and 2018, and showed that the most frequent employment sector was the production of electronic tools and devices [14]. Although battery production was the second most common occupation in the current study, this industry is also important for developing countries with higher lead blood levels in workers [15]. These findings are important in the surveillance part of occupational health and safety activities, to prioritize the risk groups for receiving planned interventions.

Before and after the treatment, lead blood level, serum creatinine, and blood urea nitrogen were statistically significantly different. Lower lead blood levels after the therapy were expected with regard to the purpose of chelation [16]. Effects of the $CaNa_2EDTA$ chelation on renal parameters has been defined as critical [9, 17]. Although this type of adverse effect is not common, the $CaNa_2EDTA$ chelation was related to elevations in serum creatinine and blood urea nitrogen [9]. However, a possible role of $CaNa_2EDTA$ chelation in slowing down the decline in renal function in patients with chronic kidney disease and lead exposure history has been documented [18]. Findings of the present study did not show any elevated results in serum creatinine and blood urea nitrogen. This may result from a well-designed treatment protocol regarding treatment goals (i.e., number of cycles and target lead blood level). Moreover, one- or two-day breaks were implemented to avoid treatments for more than five days, as advisable against nephrotoxicity [9].

Results showed a statistically significant difference in ALT, GGT, total, and direct bilirubin levels obtained before and after the treatment. Furthermore, for patients with elevated results pre-chelation, mildly elevated post-chelation results were observed in liver parameters, with the odds of any liver parameter elevated post-chelation and elevated ALT level being 9.3 and 11.4, respectively. The elevation in liver transaminases with $CaNa_2EDTA$ chelation was defined as mild, and expected to return to normal levels after the cessation of treatment [19]. A French study observed transient transaminase elevations in two of fourteen patients receiving $CaNa_2EDTA$ for lead poisoning [20]. The authors considered these elevations related to alcohol consumption in one patient and the acute nature of intoxication in the other. The current study also depicted that elevated liver parameters after the chelation therapy were related to elevated pre-chelation results. These results point out the importance of monitoring liver parameters during the $CaNa_2EDTA$ chelation in patients, particularly those with elevated basal liver parameters.

This study's strength included the evaluation of various parameters related to renal and hepatic functions, comparison of post-chelation results with those obtained before the treatment, and statistical analysis with an adjustment for parameters related

to lead exposure and chelation treatment. However, the current study has some limitations. First, results did not include intermittent measurements of renal and hepatic parameters during the course of treatment, despite the comparison of pre- and post-chelation values. Second, symptoms and signs related to chronic lead poisoning were not analyzed. Moreover, the exposure levels of patients could be related to pre- or post-chelation measurements. Although this limitation was partially eliminated by evaluating the duration of exposure, a detailed approach would be more beneficial. Lastly, due to the retrospective nature of the study, a detailed protocol with a follow-up component was not applied. Future prospective studies may overcome this issue.

In conclusion, this study documented mild elevations of liver parameters in patients after $CaNa_2EDTA$ chelation therapy, particularly those with elevated basal liver parameters, although patients' renal parameters stayed within reference ranges. These results serve as example of the safe application of $CaNa_2EDTA$ chelation for chronic occupational lead intoxication, by monitoring kidney and liver parameters in a secondary-level health facility. Future prospective studies with structured treatment protocols may investigate the risk and determinants of hepatic and renal adverse effects.

Author contribution

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

Ethical approval

This study has been conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Yuksek Ihtisas University Non-Interventional Ethics Board (Protocol no. 2021/14/01, August 25, 2021).

Funding

The author declares that the study received no funding.

Conflict of interest

The author declares that there is no conflict of interest.

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