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Case Report

Effects of Chelation Therapy on QT Dispersion in Lead Exposed Industry Workers in Turkey

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Abstract:

Occupational lead poisoning is a common and serious occupational health problem, with workers mainly exposed to lead through inhalation and ingestion. A wide range of studies conducted on lead intoxication and its ECG effects, revealed that QT interval is one of the most important parameters. QT dispersion is a marker of heterogeneity and is frequently encountered in patients with a disparity in ventricular recovery and is implicated as a direct marker of cardiovascular mortality. Battery, metal mine and car service workers who had been working in the same workplace for at least two years and admitted to Ankara Occupational Diseases Hospital for annual examination and hospitalized with toxic blood lead levels, were enrolled in the study. Patients were given chelation therapy with Ca-EDTA, and ECGs were taken before hospitalization and one week after the chelation therapy. A total of 155 male Caucasian workers (mean age = 32 ± 12 years) were evaluated. The mean blood lead level was 55.3 ± 5.1 µg/dL (min = 45.3 µg/dL max = 70.9 µg/dL). None of the participants had an arrhythmic event or death. QT dispersion before chelation and post-therapy was 38.86±13.24 msec and 35.80±12.32 msec, respectively (p=0.000001). Chelation therapy by Ca-EDTA in lead poisoning could reduce ventricular arrhythmias by homogenizing ventricular repolarization times.

1. Introduction

Cardiovascular disease is the leading cause of mortality and a primary contributor to the burden of disease worldwide [1]. Traditional risk factors such as hyperlipidaemia, hypertension, smoking, and diabetes as well as potentially preventable exposures to environmental toxicants, including lead and other metals, are factors that may explain population variations in cardiovascular disease rates [2, 3].

Lead and lead alloys have a wide range of industrial applications including leaded gasoline, industrial processes such as lead smelting, coal combustion, lead-based paints, lead containing pipes, or lead-based solder in water supply systems, battery recycling, grids and bearings [4]. Once absorbed, it is widely distributed and can be found in many tissues [5]. Occupational lead poisoning is

a common and serious occupational health problem and it leads to promoted oxidative stress and inflammation, disturbed NO signalling pathways, altered major vasoregulatory systems, damaged endothelial lining, promoted smooth muscle cell proliferation, and transformation and inhibition of fibrinolysis. Workers are exposed to lead mainly via inhalation and ingestion [6]. In Turkey, there is a legislative standard for air lead concentrations in the workplace, but there is no official standard or medical guideline for a biological exposure index. In daily practice, similar with Occupational Safety and Health Administration-USA (OSHA-USA), blood lead levels > 40 µg/dl is accepted as a threshold for critical medical care and chelation, if clinically necessary. In Turkey, the incidence of lead exposure is high due to weak preventive measures and a lack of occupational health standards.

Recent analyses suggest that health effects may become apparent at concentrations <5 µg/dl, although no evidence exists for a threshold, even at concentrations of 1 µg/dl [7]. Acute toxicity is related to occupational exposure and is quite a common issue. In general, chronic toxicity occurs when using well water or by exposure to lead-polluted air in industrial regions [8]. However, in Turkey, occupational exposure may be encountered as a result of chronic exposure, due to the above-mentioned factors. There is no conclusion regarding the exact nature of lead influence on ECG. Since the 1970's, it has been observed that lead increases myocardial sensitivity to noradrenalin and its arrhythmogenic effects and causes bradycardia via blocking beta adrenoreceptor activity [9, 10]. In various electrocardiographic studies, repolarization disorders and rhythm disturbances were observed in groups of workers who were exposed to lead, when compared to the controls [11]. Among the 775 men who participated in the Normative Aging Study, bone lead levels were found to be positively associated with heart rate, corrected QT and QRS intervals, particularly in the younger men [12]. Also, a risk of intraventricular or atrioventricular block in men with elevated bone lead levels was increased, whereas blood lead level was not associated with any of the electrocardiographic disturbances [12]. In a wide range of studies conducted on lead intoxication and its ECG effects, it was revealed that the QT interval is one of the most important parameters. As QT interval represents ventricular depolarization and repolarization, measurement of QT may help determine the period of mean ventricular action potential. QT dispersion is a marker of heterogeneity and frequently encountered in patients with a disparity in ventricular recovery. Dispersion of QT is implicated in the genesis of ventricular arrhythmias and as a direct predictor of cardiovascular mortality [13, 14].

Authors of these studies suggest that the cumulative exposure to low lead levels causes electrocardiographic conduction disturbances [15]. In light of previous studies and efforts, our aim was to determine whether there is an association between blood lead levels and chelation therapy on QT dispersion.

2. Materials and Methods

2.1 Patients

Battery, metal mine and car service workers who were admitted to Ankara Occupational Diseases Hospital for an annual examination and were hospitalized with toxic blood lead levels, were enrolled in this study. Study participants' ages were 20 - 44 years and had been working in the same workplace for at least two years.

After explaining the aim of the study, informed consents were obtained. Well-trained occupational physicians conducted patient interviews with all the participants. Then, a questionnaire containing questions regarding the patients demographic characteristics (gender, age and marital status), job-related information including history of the work causing the lead exposure and work experience, as well as respiratory disease history, intake of medicine, smoking history, leisure time, physical activity, and diet, was completed by the patients.

Body mass index (BMI) was calculated as the ratio of body weight to height squared and expressed as kg/m2. One trained physician measured the blood pressure from both arms of the study participants, while the patient was in a sitting position. After the subjects had rested for 20 mins, three measurements were taken with 5 minutes (mins) intervals, by using a standard mercury sphygmomanometer. Systolic and diastolic blood pressures were recorded as the pressures at the first and fifth Korotkoff sounds, respectively. The average of three readings was used in the data analysis [16]. Workers with a previous history of diabetes, heart or kidney diseases, malignancies, and those who were on antiarrhythmic and QT prolonging drugs were excluded.

2.2 Blood Sample Collection

Samples for blood lead levels, complete blood count and blood chemistry were analysed. The blood specimens were heated in a hot water bath at

37°C for 25 mins and homogenized by shaking for one min. Three millilitres of each of the blood samples was transferred into a Pyrex test tube. A 3:1 mixture of trichloroacetic acid (TCA 5%) and perchloric acid solution (2 M) was added into each test tube and tubes were centrifuged for 25 minutes at 3,000 rpm. The supernatant from each sample was decanted into a labelled sample bottle and the precipitate was further digested with 3.0 mL 2 M perchloric acid and centrifuged for 15 mins. The supernatant from each centrifuged sample was decanted and mixed with its corresponding supernatant from the first lysis. Finally, the lysates were stored at – 4°C until dispatched for analysis [17]. The concentration of lead in the blood samples was determined on a Flame Atomic Absorption Spectrometer (NovAA 300) at 283.3 nm after optimizing the various instrument parameters. Triplicate samples were analysed in each determination and averages of the triplicate measurements were taken for each sample. Instrument drift was checked by running the standards after analysing 10 samples. Quantification of lead in blood was carried out by using a standard lead solution with known lead concentration. Percentage recoveries determined from blood samples spiked with 10 µg of lead per 4.0 mL of blood sample were 94.6% on average. However, no correction for recoveries was performed in our data [17].

2.3 ECG Recordings

Standard resting 12-lead electrocardiograms were taken at supine position while at rest for at least for 10 mins on a SCHILLER AT102 ECG device (SCHILLER INC). QT interval was measured manually by the researchers from the beginning of the QRS complex to the end of the T wave and a corrected QT was calculated by the Bazzet's formula: QTc= QT / [RR]½. QT dispersion was calculated as the difference between the longest and the shortest QT interval on the 12 lead surfaces ECG.

2.4 Statistical Analyses

The collected data was analysed by using SPSS18 program (SPSS Inc., Chicago, IL, USA). The relationship between the blood lead levels and the statistical differences in the change on QT dispersion indices before and after therapy for lead poisoning, were analysed using a Paired

3. Results

A total of 155 male Caucasian workers with a mean age of 32 ± 12 years were evaluated. The mean blood lead level was 55.3 ± 5.1 µg/dL, ranging from 45.3 to 70.9 µg/dL. The mean working years were 3.7 ± 1.1 years. Patients were given chelation therapy with Ca-EDTA and ECGs were taken before hospitalization and 1 week after chelation. Demographic characteristics of the participants are shown in Table 1. Alcohol consumption rate was 6.45 %, while the smoking rate was 66.46 % among workers. Medical history of 11 participants included the hypertension diagnosis. None of the study participants were on medical therapy that prolongs QT interval on surface ECG and none of the participants experienced arrhythmic event or death during hospitalization.

Table 2 indicates the QT dispersion before and after chelation therapy for lead poisoning. Two QT dispersion measurements were taken from participants, one was at the time of the hospital admission and the second was before hospital discharge. QT dispersion before chelation therapy was measured as 38.86 ± 13.241 msec and there was a statistically significant difference between post-therapy measurements that were 35.80 ± 12.32 msec (p = 0.000001).

Table 1. *Demographic values and disease history of the participants.*

Gender	Male 155 (100%)
Age (years)	32.83 years
Marital status (married)	97 (62.58 %)
Smoking	
Non-smoker	35 (22.58 %)
Ex-smoker	17 (10.96 %)
Smoker	103 (66.46 %)
Blood pressure	
Systolic (mean)	124.7 mmHg
Diastolic (mean)	76.5 mmHg
BMI	22.7 kg/m²
History of dyslipidaemia	18 (11.6 %)
History of hypertension	11 (7.09 %)
Alcohol consumption	10 (6.45 %)

Table 2: *Effect of chelation therapy on QT dispersion times*

	Before chelation	**After chelation**	**p**
QT dispersion times	38.86±13.24 msec	35.80±12.32 msec	0.000001

4. Discussions

Lead may cause cardiovascular effects by altering the renin-angiotensin system, activating the sympathetic system, changing the homeostasis of

electrolytes, and inducing free radical production that lead to direct endothelial dysfunction [10, 18-20].

QT prolonging, arrhythmogenic, cardiotoxic, accelerated atherosclerosis and hypertensive effects of lead are well-known and are widely studied subjects of both toxicology and cardiology. Fifteen studies reported the association of lead with other electrocardiographic parameters but only three of them investigated the potential effects of lead on QT interval [12]. In 1990 in Poland, Sroczynski et al. conducted a study of 711 industrial workers exposed to lead and concluded that as the blood lead levels increased the prevalence of ventricular repolarization changes also increased [21]. Another study designed by Gatagonova et al. recruited lead workers in Russia and found that the incidence of P wave, QT and QRS interval changes increased by increasing lead levels [22].

All studies, except the Normative Aging Study, were conducted on the occupational populations in Europe. These types of outcome including rhythm disorders, ischemic changes and cycle duration, varied widely across studies, and the findings were inconsistent. Normative Aging Study conducted by Chenget al. [12] in a subgroup of people in which higher concentrations of lead in the blood were detected, researchers pointed out the prolonged QRS interval and disturbances in intracellular conductivity in people over 65 years, and the increased risk of atrioventricular block in people over 65 years. Notably, the American National Health and Nutrition Examination Surveys (NHANES) have consistently demonstrated increased mortality associated with lead exposure [23]. Based on the information obtained from NHANES III, the mortality from all-cause, cardiovascular disease and cancer was increased by 59 %, 55 % and 69 %, respectively, in people with blood lead levels (BLL) over 10 mg/dL compared to the people with BLL of <5 mg/dL [23]. Alarmingly, even populations with BLL between 5 and 9 mg/dl had a higher mortality than populations with a BLL lower than 5 mg/dL [23].

There are very few surveys related to lead exposure in Turkey. In a survey of traffic policemen in Bursa, the average lead blood level was 9.4 µg/dL [24], while among the battery workers in Gaziantep the average level was 36.83 µg/dL [25], and in apprentices working in Bursa conducted by Pala et al., the average level was 4.99 µg/dL [7]. In other Turkish surveys regarding the BLL of apprentices, the average blood lead levels were 7.6 µg/dl in Isparta [26], and 27.8 µg/dl in Sanliurfa [27]. On the other hand, blood lead levels were higher in our study when compared to the above-mentioned studies and were 55.3 ± 5.1 µg/ dL, ranging from 45.3 to 70.9 µg/ dL.

5. Conclusions

None of the above-mentioned studies evaluated the effects of chelation therapy on the ECG parameters in patients with lead poisoning. Our findings revealed that the chelation therapy with Ca-EDTA decreases the QT dispersion times and forms a homogeneous repolarization of the ventricle. Several large prospective studies published assessed the predictive value of QT dispersion for cardiac and all-cause mortality in the general population.

As dispersion of QT is implicated in the genesis of ventricular arrhythmias, chelation therapy by Ca-EDTA in lead poisoning could reduce ventricular arrhythmias by homogenizing ventricular repolarization times, by reducing QT dispersion times. On the other hand, further large-scale studies on the effects of chelation therapy on cardiovascular mortality can provide more useful information.

Author Statements:

- The authors declare that they have equal right on this paper.
- The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper
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