The changes of lead exposed workers' ECG and blood pressure by testing the effect of $CaNa_2EDTA$ on blood lead

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Abstract: The role of lead pollution in the induction of hypertension and electrocardiogram (ECG) changes has not been sufficiently recognized. The present study is aimed to calculate the association between lead exposure and blood pressure (BP) and ECG findings. A group of 147 lead-exposed workers from a battery plant and 104 controls were examined for blood lead levels (PbB), BP, and ECG. The exposed workers were followed annually from 2008 to 2010. Furthermore, lead in air dust and fumes were also detected in the breathing zone of the workplace. The PbB of lead-exposed workers were correlated with air lead in worksites from 2008 to 2010. A linear regression of repeated measurement analysis showed that diastolic blood pressure (DBP) in exposed workers decreased consecutively from 2008 to 2010 ($p<0.01$) with reduced lead exposure; however, this value was not correlated with the incidence of hypertension ($p=0.138$). Abnormal ECG rates were 35.37%, 38.78%, and 44.90% in 2008, 2009, and 2010, respectively, demonstrating an annual increase ($p=0.024$). Our study showed that lead exposure was crucial factor in causing ECG abnormalities. No correlation was identified between lead exposure and hypertension, and further study is needed. EDTA for the treatment of blood lead object on lead poisoning (PbB) level, abnormal electrocardiogram and blood pressure increases curative effect, and the better effect of the longer range.

Keywords: Lead exposure, blood lead, electrocardiogram, hypertension, lead expelling.

INTRODUCTION

Lead is an important material used widely in many industries, including battery, paint, ceramic and tile factories. Lead is known to be associated with several diseases in the kidneys as well as the nervous, skeletal, immune, gastrointestinal, and reproductive systems (Glenn *et al.,* 2003). Recently, studies have revealed the role of lead pollution in the induction of hypertension, peripheral arterial disease, and circulatory and cardio-vascular mortality (Peters *et al.,* 2012; Weisskopf *et al.,* 2009). Thus, increasing attention has been paid to the impact of lead exposure on the pathogenesis of circulatory system disease.

The relationship between occupational exposure to lead and abnormalities in blood pressure (BP) and electrocardiogram (ECG) results remain poorly recognized (Glenn *et al.,* 2006; Cosselman *et al.,* 2015; Hara *et al.,* 2015). Recently, animal studies have shown interesting biphasic results, indicating low lead levels decrease BP, while higher lead doses increase BP in rats (Wildemann *et al.,* 2015). However, inconsistent results have been obtained regarding the effects of lead exposure on workers' BP and ECG findings. Some studies have found a correlation between elevated systolic (SBP) and/or diastolic blood pressure (DBP) with increased lead exposure, while others reported weak or no associations (Neri *et al.,* 1988; Glenn *et al.,* 2003). Thus, an improved understanding of the relationship between lead exposure and BP or ECG findings in epidemiological studies is needed.

In the present study, continuous occupational health examinations from 2008 to 2010 were conducted in a lead battery plant in Anhui province in China, and the results showed that the blood lead (PbB) levels in workers exposed to a high-lead environment were associated with ECG abnormalities.

In China, the medicine for expelling lead include EDTA, calcium disodium edetate, sodium dimeraptosuccinate (DMS), diethylene triamine pentacetic acid (DTPA), penicillamine, and testes drug, pineapple peel extract of apple pectin. Na_2 Ca(edta) solution was injected with a chemical masking agent EDTA, which was used to treat lead poisoning. This is due to $(Ca(edta)^{2-}$ complex ion dissociated ($edta^{4-}$ can lead complexation with the human body. $(edta)^{4-}$ produced $(Pb(edta)^{2-}$ complex ion that was more stable than $(Ca(edta)^{2-}$ and can be excreted from the body.

MATERIALS AND METHODS

Subjects

Exposed workers were recruited during routine medical surveillance at a battery plant in Wuhu, Anhui province in China. This factory mainly produces lead acid batteries using a procedure comprising casting, smearing, formation, division, and assembly, which produces lead, sulfuric acid and noise pollutions as occupational hazards (Glenn *et al.,* 2003). To investigate lead exposure, 147

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workers with potential lead exposure in the plant were recruited as an experimental group for the study in 3 consecutive years from May-June, 2008 to 2010. These subjects included 95 males and 52 females aged from 19 to 56 years (average age at 37.51±6.75 years) with a duration of lead exposure 1 to 22 years (average of 4.56±3.24 years) in 2008, as shown in table 1. A total of 104 health workers without lead exposure (average age of 36.88±9.39 years) were recruited from the casting factory as the control group in the year 2008, but without follow up. Anticoagulated blood samples were collected from all participants during routine medical surveillance. The study protocol was approved by the Research Ethics Review Board of First Affiliated Hospital of Zhengzhou University.

Lead exposure assessment

Lead exposure assessment included the detection of air lead in the workplace and PbB levels. The air samples were collected from all potential lead-polluted worksites at working times when all machines were in normal operation, according to the sampling standard of China GBZ 159-2004 (Sampling Standard for Monitoring Harmful Substances in Workplace Air). The air samples were collected within the breathing zone of the workers three times a day at 9:00, 11:00 and 16:00, at a rate of 0.1 L/min for 30 minutes using the IFC-2 dust sampler (Hongyu, Shanghai, China). Flame atomic absorption spectrometry (WYX-9003, Yitong, Shenyang) was used to detect the air lead concentration.

The differential potentiometric stripping method (PbU-DPSA method) was used to determine the PbB levels. According to the cut-off point of the occupational chronic lead poisoning diagnostic standard (GBZ37-2002), the range of abnormal PbB concentrations was ⩾400 g/L.

Health surveillance

BP, ECG, hemogram, and routine urine analysis of each participant was performed during a health examination. An automated hematology analyzer (XE-2100, Sysmex, Japan) was used to detect the hemogram. A Riva-Rocci sphygmomanometer was used to measure BP; prior to measurement, each participant was required to sit for 5 minutes, all measurements were obtained from 8:00 to 10:00 in the morning. The workers were divided into three groups (normal, borderline hypertension, and diagnosed hypertension) according to their BP results. Normal BP is defined as a SBP at or below 140 mmHg and DBP at or below 90 mmHg; borderline hypertension ranges from SBP between 141-179 mmHg and DBP between 91-109 mmHg; and diagnosed hypertension involves a SBP at or above 180 mmHg and DBP at or above 110 mmHg. An ECG was performed, and the abnormalities were divided into the following categories: early repolarization, left ventricular voltage increase, ST segment elevation, and sinus bradycardia. In addition, the BP measurements and ECG findings were performed by the same doctors in the same hospital for all three years of the study.

The chemical name of $CaNa_2EDTA$ is disodium calcium ethylene diamine tetraacetate (Glenn *et al.,* 2006). In the experimental process, we injected sodium calcium carbonate for treating lead poisoning, and its dosage form is 1000mg/bottle. The drug was treated by using interval therapy method; we added 1.0g sodium calcium carbonate was to 250-500ml glucose solution, for 1 day's treatment. After the preliminary investigation, researchers selected 36 people from lead poisoning, to be given to the 20% intravenous injection of EDTA injection. And we make comparisons of blood lead level (PBB), blood pressure and electrocardiogram at different time points after treatment.

STATISTICAL ANALYSIS

EpiData 3.0 was used to establish the database, and Statistics package SAS (Version 9.1) was used for statistical analysis. We analyzed basic parameters (mean ± standard error) to express BP, ECG, and hemogram for data with a normal distribution, while the median (range) was used to describe non-normally distributed data. The correlation between worksite air lead concentration, PbB level, and BP was analyzed, and the trend text was used to calculate the three years of repeated measurement data. For quantitative variables, arithmetic means and standard deviations of the parameters were calculated in the studied groups. The results for categorical variables were expressed as percentages. The subsequent statistical analysis of independent qualitative variables took advantage of the chi-square test (maximum likelihood method). All the parameters, including hemogram and abnormal BP, were measured by linear regression of repeated measurement analysis. Significance was set at $p < 0.05$.

RESULTS

Elevation of PbB by air lead pollution

As shown in table 2, the median and range of ambient air lead concentrations varied from 0.145 (0-1.035), 0.017 (0.010-0.330) and 0.020 (0-0.330) (mg/m3) across worksites in the factory in 2008, 2009, and 2010, respectively. According to the occupational exposure limit of China (GBZ2.1-2007), 15, 5, and 7 worksites from the 24 detected sites were failed to comply in years 2008, 2009, and 2010, respectively. Compared to the control group (55.35±37.48μg/L), the PbB of the lead-exposed group (n=147) was 847.47±423.89μg/L, 334.82±140.84 μg/L and 431.23±190.75μg/L, respectively, in 2008, 2009 and 2010, indicating that the workers were severely lead poisoned. Furthermore, there were strong correlations between the PbB and air lead levels in the workplace; PbB increased significantly with the elevation of air lead with correlation coefficients of 0.569, 0.559, 0.402 in

2008 (p<0.01), 2009 (p<0.01) and 2010 (p<0.01), respectively.

Impact of lead exposure on hemogram, BP and ECG

To address physiological changes, the hemogram indexes were analyzed, and the results in table 3 show that white blood cells, erythrocytes, hemoglobin, and platelets in lead-exposed workers in 2008, 2009 and 2010 were significantly higher than those in the control group (p<0.01). Moreover, SBP and DBP levels in the controls were significantly lower than those in lead-exposed workers in 2008 (p<0.01). The linear regression of repeated measurement analysis showed that the DBP and white blood cell count of exposed workers decreased consecutively from 2008 to 2010 (p<0.01). However, there was no correlation between PbB and SBP or DBP for the three years studied (data not shown).

Table 4 shows that the hypertension rates (borderline hypertension and hypertension) in all three years were higher than those in the control group; however, over the 3-year period, no significant decreased trend was observed in the hypertension rate (p=0.138).

The abnormal ECG rate was significantly lower in controls (5.8%) than in exposed workers (35.37%) in 2008 (table 5). Repeated measurement of quantitative data analysis showed that the abnormal ECG rate (2008, 2009, 2010: 35.37%, 38.78%, 44.90%) of exposed workers increased consecutively from 2008 to 2010 (p=0.024) (table 4).

Elevation of PbB, blood pressure and electrocardiogram

The level of blood lead (PbB) after treatment for 3 months was 494.70±28.77g/L, and the level of blood lead (PbB) was about 382.82±46.61 g/L (p=0.001). The abnormal rate of ECG was 39.96% in the treatment group for 3 months, and the rate was about 33.11% (p=0.003) after the treatment for 6 months. The abnormal rate of blood pressure was 3 in the treatment group at the end of 21.24% months, and the rate of blood pressure was about 15.18% (p=0.006) after treatment for 6 months (table 5).

DISCUSSION

Our results showed that workers in a battery plant in Wuhu, Anhui province were exposed to high air lead concentrations, and their PbB concentrations from 2008 to 2010 were higher than the accepted safe level based on the Chinese Occupational Chronic Lead Poisoning recommendations (GBZ37-2002). Hemogram changes can be considered the most obvious biological effects of lead on health. Significant decreases in white blood cells, erythrocytes, hemoglobin, and platelets have been observed in lead-exposed workers. A linear regression of repeated measurement analysis showed that white blood cell levels were reduced consecutively from 2008 to 2010 (p<0.01), which was consistent with the findings of a previous study (Cabaravdic, 2010).

Studies of the association between lead exposure and the increased incidence of hypertension and cardiovascular diseases have been reported since the early 20th century (Rapisarda, 2015). However, additional epidemiologic study is needed to confirm these results. In the present study, the SBP and DBP levels in the control group were significantly lower than those in lead-exposed workers in 2008. This result demonstrated increased BP in lead-exposed workers, although this was not associated with the rate of hypertension from 2008 to 2010. The mean DBP increased slightly from 2009 to 2010, which is consistent with the trends of PbB and air lead concentration. Our findings further showed that long-term occupational exposure to lead was related to slight increases in SBP and DBP among workers, although the impact was likely a transient increase in BP and did not produce sustained BP elevation. This result is consistent with previous studies (Taheri, 2014). During the first two cycles of the Canadian Health Measures Survey with 4,550 respondents, a modest association emerged between PbB levels and SBP among 40- to 54-year-olds, whereas no association was detected between PbB levels and hypertension prevalence. Azusa *et al* also reported that PbB doubling was associated with higher SBP and DBP but not with the prevalence of hypertension (0.95; 0.90-1.01; p=0.11), based on the National Health and Nutrition Examination Survey (2003–2010).

Other studies have also assessed individual lead effects but have reported conflicting results. Ladan *et al*. evaluated 200 male battery factory workers and found no association between PbB and SBP and DBP. In the longitudinal (1985-1995) Public Health and Environmental Exposure to Cadmium study (PheeCad) in Belgium (Staessen, 1996), there was no consistent association between changes in conventionally measured BP or the incidence of hypertension and changes in PbB or zinc protoporphyrin (Hara, 2015). However, there have been a number of reports showing increased mean values of SBP and DBP in lead-exposed individuals. The overall pattern of results in those studies suggest that occupational exposure to lead can be associated with increased BP and accelerated progression of atherosclerosis (Poreba, 2011; Were, 2014). Furthermore, between 1988 and 1994, the National Center for Health Statistics conducted the third NHANES (NHANES III), and the results showed that SBP variability was significantly associated with environmental lead exposure after adjusting for the effects of confounders (Faramawi, 2015). In addition, Poręba *et al* demonstrated that among persons with arterial hypertension, occupational exposure to lead increased the blood zinc protoporphyrin concentration, which was taken as an independent risk factor for increased BP. In Taiwan, Kuo *et al* reported that PbB were positively correlated with both SBP and DBP after adjusting confounding factors among 2,565 adults.

Table 1: Characteristics of lead-exposed workers and controls in 2008

Group	Exposed worker number (%)	Control number (%)
Gender		
Male	97 (64.6)	62 (59.6)
Female	52 (35.4)	42 (40.4)
Age	37.51±6.75	36.88±9.39
Smoking		
Non-smoker	121 (82.3)	85 (81.7)
Smoker	26 (17.7)	19 (18.3)
Drinking		
Non-user	90 (61.2)	73 (70.2)
User	57 (38.8)	31 (29.8)

Table 2: Association between blood lead and air lead concentration over three years

Year	Blood lead (μg/L)	Worksites (unqualified sites)[a]	Lead concentration (mg/m3)	
			Range	Mean ± SD
Control	55.35±37.48	---	---	---
2008	847.47±423.89	24 (15)	0 - 1.035	0.356±0.353
2009	334.82±140.84*	24 (5)	0.010-0.330	0.035±0.072*
2010	431.23±190.75*#	24 (7)	0-0.330	0.039±0.72*

a The maximum harmful permissible concentration of lead dust in the air of worksite was less than 0.05 mg/m3 as qualified according to the standard in China (TJ36-79). *compared to the year 2008, p<0.05. # compared to the year 2009, p<0.05.

Table 3: Association between blood lead and hematologic data and systolic and diastolic blood pressure over three years

	White blood cells (×109/L)	Erythrocytes (×1012/L)	Hemoglobin (g/L)[b]	Platelets (×109/L)	Systolic pressure (mmhg)	Diastolic pressure (mmhg)
Control	6.45±1.43	4.87±4.73	148.13±14.78	221.27±43.76	136.5±13.5	89.9±11.1
2008	5.71±1.82	4.63±0.59	138.82±18.16	158.96±40.87	159.1±16.8	103.4±12.3
2009	5.75±1.61	4.30±0.51*	128.54±17.25*	159.76±40.53	153.0±18.0	98.1±12.7
2010	5.46±1.50	4.43±0.65*	126.67±20.58*	158.90±37.80	156.1±18.8	98.5±14.0
Number	147	147	147	147	132	132
F value [a]	9.38	1.84	1.03	2.12	2.44	3.52
p value [a]	0.003	0.177	0.311	0.148	0.121	0.032

a Data were measured by linear regression of repeated measurement analysis after adjusting for the factors of age, gender, smoking and drinking, and Dunnett's test was used to compare the two groups. b Linear regression of repeated measurement analysis found that gender (female) was the leading influencing factor for hemoglobin (F=24.03, p<0.001). *compared to the year 2008, p<0.05.

Table 4: The comparison of abnormal blood pressure rates in lead-exposed workers and controls

Hypertension groups	Control (%)	2008(%)	2009(%)a	2010(%)
Normal group	75(72.1)	9 (6.1)	23(15.6)	14(9.5)
Borderline hypertension	21(20.2)	88(59.9)	83(56.5)	86(58.5)
Hypertension group	8(7.7)	50(34.0)	40(27.2)	46(31.3)
Missed	0	0(0)	1(0.7)	1(0.7)
Total	104	147	147	147
X^2	107.4 [b]		6.97 [c]	
P	<0.001 [b]		0.138 [c]	

The workers were divided into three groups (normal, borderline hypertension, diagnosed hypertension) according to blood pressure; detailed information is provided with the methods. a compared to the year 2008, X2=6.49, p=0.039. b Data were derived from the Chi-squared test between the control and year 2008. c Data were measured by repeated measurement analysis of categorical data.

Table 5: Elevation of PbB, blood pressure and electrocardiogram (n=36)

Index	3 months(g/L)	6 months(g/L)	P
PbB	494.70±28.77	382.82±46.61	0.001
the abnormal ECG rate	39.96%	50.89±8.21	0.003
the abnormal BP	21.24%	15.18%	0.006

Our findings show that long-term occupational exposure to lead is strongly related to abnormal ECG results, with a consistent increased incidence of abnormal ECG results from 2008 to 2010. The results of the present study are consistent with data from previous epidemiologic studies. Sung *et al*. found evidence that low-level lead exposure was associated with a prolonged QT interval. Ki-Do *et al*. suggested that low-level cumulative exposure of lead was associated with worse future cardiac conductivity in the ventricular myocardium from a prospective cohort study (a cohort study of aging established by the U.S. Veterans Administration (VA) in 1963). Furthermore, in contrast to those reports, the PbB level in our exposed workers was far higher than that in a natural environment.

The toxicity of calcium disodium two was slightly lower than that of heavy metal chelating agent, which could not only promote the excretion of lead, but also compete with the ligand *in vivo*, such as enzyme system. After injection, the peak of urinary excretion was within 24h, which is one of the first-choice drugs for the treatment of lead. However, the drug has a high calcium content of calcium salt, and has a greater stimulating effect on blood vessels and muscles. Therefore, intravenous injection should be diluted with 5% glucose solution into the 0.1%-0.2% concentration, drip should be avoided when the extravasation of blood vessels, otherwise easy to cause inflammation of the blood vessels or local necrosis.

CONCLUSION

These findings may have important implications for the prevention of chronic lead poisoning in lead-exposed workers. However, there are also several limitations to our study. First, the number of exposed workers was not large enough to fully analyze the health effect of lead exposure. In addition, other factors, such as noise and sulfuric acid mist, were not considered in our study. However, the prospective study design and repeated measurement over three continuous years represent strengths of this study, as the effect of individual differences can be eliminated by self-control through repeated measurement data analysis.

In conclusion, our findings indicate that PbB levels can independently contribute to abnormal ECG rates. Our results further showed that BP and hypertension in the lead-exposed group were higher than in the control group, although we did not find an increased hypertension rate during repeated measurements over three years from 2008 to 2010, which indicates that further research is needed to confirm our results. EDTA for the treatment of blood lead object on lead poisoning (PbB) level, abnormal electrocardiogram and blood pressure increase curative effect, and the better effect of the longer range.

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