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Dose-response relationship between blood lead levels and hematological parameters in children from central China

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ABSTRACT

Background: Lead is a heavy metal that can affect the human hematological system. However, reports are limited on the dose-response relationship between blood lead levels (BLLs) and hematological parameters in children. This study aimed to explore the dose-response relationship between BLLs and hematological measurements among children in China.

Methods: A cross-sectional design was used. A total of 743 children aged 5–8 years were recruited from two counties in central China. The BLLs and blood levels of iron, zinc, and calcium were determined, and hematological parameters were measured.

Results: All hematological measurements and BLLs were logarithm-transformed to ensure a normal distribution. The geometric mean of the BLLs of all children was 82.4 μg/L. Forty-one percent of the children had BLLs ≥ 100 μg/L. The lead-poisoning percentages of the children were significantly associated with gender, age, district of residence, and environmental lead exposure level. Multivariate linear regression analyses showed no significant linear correlation between BLL and each hematological parameter among the children with BLLs ≥ 100 μg/L. The analyses also revealed a small increase in red blood cell count (RBC) with increasing BLLs in the BLLs < 100 μg/L group ($\beta = 0.03$, $P = 0.048$). A negative association was noted between BLLs and blood platelet (PLT) count in the children with BLLs < 100 μg/L ($\beta = -0.90$, $P < 0.001$). Logistic regression analyses showed that BLLs were significantly associated with decreased hemoglobin (Hb) levels, RBC counts, PLT counts and mean corpuscular hemoglobin (MCH) after adjusting for potential confounders. Such analyses also revealed a dose-response relationship between the BLLs and hematological parameters (Hb level, RBC count, and PLT count). The children with BLLs ≥ 100 μg/L were 2.72, 2.51, and 3.76 times more likely to achieve decreased RBC counts, Hb levels and PLT counts, respectively, compared to those with BLLs < 100 μg/L. Compared with children with BLLs < 100 μg/L, those with BLLs ≥ 100 μg/L were 3.16 and 4.38 times more likely to show decreased Hb levels and PLT counts respectively in the high-level lead-exposure group and 4.33 times more likely to achieve a decreased PLT count in the low-level lead-exposure group. The individuals with BLLs of the highest quartile were 3.65, 5.87, and 29.23 times more likely to exhibit decreased Hb levels, RBC counts, and PLT counts, respectively, than the children with BLLs of the lowest quartile.

Conclusion: Our findings suggested a negative association between BLLs and hematological indicators (Hb level, RBC count, PLT count and MCH). A strong negative, non-linear dose-response relationship was also showed between BLLs and hematological parameters (Hb level, RBC count, and PLT count).

1. Introduction

Lead is a heavy metal that adversely influences childhood intelligence, growth, and hearing and can cause anemia, attention deficits, and behavioral problems (Gao et al., 2001; AbuShady et al., 2017; Pan et al., 2017). Compared with adults, children are more susceptible to lead effects because of their frequent hand-to-mouth behavior, high gastrointestinal absorption rate of lead, elevated turnover of bone lead into blood, and immature organs and defense mechanisms (Bas et al., 2012; Leggett, 1993; Keller et al., 2017). Some governments have phased out the use of leaded gasoline and hence substantially reduced the content of atmospheric lead deposition in soils (Schmidt, 2010).

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Even so, environmental lead pollution and the consequent health impairment in children remain as important issues in some regions (Ahamed et al., 2007). Human-beings are exposed to environmental lead through contaminated water, food, house dust, and industrial activities such as metal recycling and battery production (Barbosa et al., 2005; Safruk et al., 2017).

The Centers for Disease Control and Prevention defined 100 μg lead/L blood as the lead level of concern for children (Gao et al., 2001). However, the safety threshold of lead exposure remains uncertain in this population. Lead is harmful to various organ systems, including the hematological system. Lead can inhibit heme synthesis and hence cause anemia. Ahamed et al. (2007) found that children with blood lead levels (BLLs) $\geq$ 100 μg/L were 2.87 times more likely to suffer from anemia than those with BLLs $<$ 100 μg/L. A cross-sectional study suggested that BLLs close to 1.21 μmol/L (250 μg/L) were associated with dose-related depression of hematocrit (HCT) in young children (Schwartz et al., 1990). Terayama (1993) reported that lead exposure significantly decreased the red blood cell (RBC) count, hemoglobin (Hb) level, HCT, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), as well as shortened the erythrocyte survival time. A study on blood lead and its effect on the Cd, Cu, Zn, Fe, and hemoglobin levels of children showed a decreasing trend in Hb content with increasing BLLs among Mumbai children (Tripathi et al., 2001). BLL was reported to be inversely and independently related to erythropoietin concentration (Liebelt et al., 1999). Bergdahl et al. (1999) demonstrated that the Hb concentrations were associated with BLLs among children with either low or high lead exposure levels; free erythrocyte protoporphyrins in the blood were also associated with BLLs. However, a study in children aged 5–14 years found that increasing BLLs by 10 μg/L was associated with a small rise in the number of RBCs and reduced MCV and MCH among girls with low BLLs ($<$ 100 μg/L) (Jacob et al., 2000).

To the best of our knowledge, the dose-response relationship between BLLs and hematological parameters has not been elucidated. On the basis of epidemiological study on the lead exposure of children in central China, this article aimed to evaluate the dose-response relationship between BLLs and hematological parameters.

2. Materials and methods

2.1. Study area

Participants were recruited from two areas in central China. One area was county X in X city (112°00′N, 31°54′E) located northwest of Hubei Province. We selected two villages that we designed as SH and I in county X. A storage battery plant built in 1980 is present in the village SH. This plant occupies about 30,000 m^2 land area and employs about 1790 workers. Village I lies about 12 km away from the storage battery plant. According to one of our previous study, the children are exposed to environmental lead at a comparatively higher level in village SH than those in village I (Li et al., 2016). Hence, the children recruited from villages SH and I were categorized into the high-level and low-level lead-exposure groups, respectively, in this study. The other study area was county Y in C city (113°12′N, 25°46′E) and located southeast of Hunan Province. A large-scale lead-zinc mine is situated in county Y and extends to about 5210,000 m^2 land area with about 1400 employees. The participants in county Y were selected from two boarding schools located about 30 and 0.8 km, respectively, away from the mine. Similarly, children are exposed to environmental lead at higher-level in the school 0.8 km away from the mine than in the other school (Li et al., 2016). The subjects from the former were designated to the high-level lead exposure group, whereas those from the latter were designated to the low-level lead exposure group.

2.2. Study design and subjects

A cross-sectional study design was adopted in this study. All participants were selected from the Blood Lead Intervention Program (BLIP), which was conducted to assess the effects of environmental and behavioral interventions in childhood BLLs. The BLIP began in December 2012 and continued for about 5 years. Children aged 5–8 years were sampled from county X and county Y by cluster sampling. A total of 758 subjects including 431 from county X and 327 from county Y were recruited in the study. We excluded subjects without complete data for basic demographic information, BLLs, or basic hematological parameters (Hb, RBC, white blood cell (WBC), and PLT). Finally, 743 subjects remained in this study.

All participants and their guardians signed informed consent. This research was approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology.

2.3. Sample detection

After disinfection of the venipuncture site with 70% alcohol, up to 2 ml of whole blood was drawn from each participant through arm venipuncture. Hematological parameters were determined from fresh samples drawn into 2 ml purple-top vacutainer tubes with EDTA. Hematological parameters were analyzed by an automated hematology analyzer (BC-5800; Mindray, Shenzhen, China) with quality control processes. The instrumental background ranges were ≤ 1 g/L, $\leq 0.03 \times 10^{12}$/L, $\leq 0.3 \times 10^9$/L and $\leq 10 \times 10^9$/L for Hb, RBC, WBC and PLT, respectively. The blood sample were frozen immediately and stored at -80 °C. Blood lead was determined using a graphite furnace atomic absorption spectrometer (Li et al., 2016), in accordance with WS/T20–1996 in China. Blood iron, zinc and calcium levels were analyzed by flame atomic absorption spectrometry using corresponding hollow cathode lamps (248.3, 213.9, and 422.7 nm for iron, zinc, and calcium, respectively) (Ahamed et al., 2007). Detection limits were 0.5 μg/L for lead, 0.002 mg/L for zinc, 0.02 mg/L for calcium and 0.018 mg/L for iron. Methods for measuring environmental lead exposure levels were described in another study conducted by our laboratory (Li et al., 2016). Following World Health Organization recommendations, the reference Hb range was 115–160 g/L for children aged 5–11 years. (Chan, 2011). Meanwhile, other relevant sources recommended the following reference ranges for WBC counts, PLT counts and MCH: $(4-10) \times 10^9$/L, $(100-300) \times 10^9$/L, and 27–33 pg, respectively (Wu, 2003). The recommended reference ranges for RBC counts were (4.0–5.5) $\times 10^{12}$/L for boys and (3.5–5.0) $\times 10^{12}$/L for girls (Wu, 2003).

2.4. Statistical analysis

All statistical analyses were performed with the SPSS software (version 21.0). BLLs and hematological parameters were log-transformed to ensure a normal distribution. We performed chi-square test and Mann-Whitney *U* test to compare BLLs among participants by gender, age, district, and environmental lead exposure level. Multivariate linear regression modeling was conducted to explore the associations between BLLs and hematological parameters while controlling for covariates, such as age; gender; lead-exposure level; body mass index (BMI); and serum iron, zinc, and calcium levels. Logistic regression was performed to obtain crude and adjusted odds ratios (*ORs*) (with corresponding 95% confidence intervals (*CIs*)) of decreased hematological parameters (i.e., Hb, RBC, WBC, PLT and MCH) in relation to BLLs. The Hb values of $>$ 160 g/L were regarded as outliers and ruled out from the analyses of HB. A Hb value of below 115 g/L was regarded as decreased Hb, and that within 115–160 g/L was regarded as normal. The other hematological parameters such as RBC count, WBC count, PLT count and MCH were converted into categorical variables by utilizing corresponding thresholds. Backwards maximum