Abstract

**Background** Lead is a harmful toxin that affects human health worldwide, especially in children. Lead poisoning remains a global problem both in developed and developing countries. The Centers for Disease Control and Prevention (CDC) recommends nutritional intervention with iron supplementation to efficiently control high lead levels. Iron supplementation in the form of sodium ferric ethylene-diaminetera-acetic acid/ ferric sodium edentate (NaFeEDTA) is highly bioavailable.

**Objective** To determine the effectiveness of ferric sodium edentate (NaFeEDTA) on lead levels in children with lead poisoning.

**Methods** This interventional, analytical study, had a one group pretest-posttest design, and was done on children in four elementary schools in the Talawaan District, North Minahasa Regency, Manado, North Sulawesi, from August to November 2014. Inclusion criteria were elementary students aged 6-9 years with lead poisoning (lead levels ≥ 10 μg/dL) and good nutritional status. Subjects were given NaFeEDTA 115.4 mg (15 mg elemental iron) at a dosage of 3 mg/kgBW/day elemental iron given between meal times. Iron supplementation was given daily per oral route for 12 weeks. Descriptive analysis was used to analyze the characteristics of the study sample. Pre- and post-test analyses were done with paired T-tests. Significance level was P <0.05.

**Results** In this study, 39 children met the inclusion criteria and consisted of 19 boys and 20 girls. Their mean age was 8.43 (SD 0.44) years. Pre-test and post-test blood lead levels was 36.18 μg/dL and 5.22 μg/dL, respectively. There was a significant reduction in mean blood lead levels after administration of NaFeEDTA (P <0.0001).

**Conclusion** In children with lead poisoning, blood lead levels are significantly reduced after 12 weeks of NaFeEDTA supplementation. [Paediatr Indones. 2017;57:171-5; doi: http://dx.doi.org/10.14238/pi57.4.2017.171-5].

**Keywords:** lead poisoning; blood lead levels; NaFeEDTA

Lead is a harmful toxin that affects human health. In children, lead can cause decreased level of intelligence (IQ points), decreased learning ability, impaired growth and hearing, anemia, as well as conduct disorder/attention and behavior problems. Currently, lead contamination occurs everywhere. Lead poisoning in Indonesia is thought to come from various sources, such as leaded gasoline, paint, vegetables, fertilizers, and other sources. Blood lead level is the gold standard for determining its effect in the blood. The Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP), and several national and international organizations have established that blood lead levels of >10 μg/dL are considered to be lead poisoning.1,2,3 In some large cities in Indonesia,
35.4 to 90% of children have blood lead levels >10 μg/dL. Iron is an important metal substitution target of Pb2+. At the molecular level, iron deficient children have increased expression of the divalent metal transporter 1 (DMT-1) in the duodenum, in order to increase iron absorption. However, lead absorption can also increase in these children.4,5 One month of iron supplementation in children with iron deficiency anemia was proven to decrease blood lead levels. The CDC recommends nutritional intervention with iron supplementation to control high blood lead levels. Iron supplementation in form of ethylenediaminetetraacetic acid ferric sodium / ferric sodium edentate (NaFeEDTA) has a high bioavailability. Content of EDTA in NaFeEDTA increased the bonding of minerals from blood, one of them is lead.6,7 The aim of this study was to evaluate the effectiveness of ferric sodium edentate (NaFeEDTA) supplementation on decreasing blood lead levels in children with lead poisoning.

Methods

This analytic, interventional study had a one-group, pretest-posttest design. The study was conducted in four elementary schools located in the Talawaan District of North Minahasa Regency, Manado, North Sulawesi, from August to November 2014. Subjects were aged 6-9 years, with blood lead levels ≥ 10 μg/dL, the established cut-off for diagnosing lead poisoning.1 Inclusion criteria were students with lead poisoning (≥ 10 μg/dL), good nutritional status based on the 2000 CDC growth charts, and normal hemoglobin (Hb) level (Hb ≥ 11 g/dL). Exclusion criteria were students with fractures, infections such as runny nose, cough, or diarrhea, high fever within the three consecutive days before blood specimens were taken, concomitant diseases such as renal or liver disease, infections that needed a long period of treatment such as tuberculosis, tumors, history of blood abnormalities or acute bleeding in the three months prior to the study, or those who took iron supplementation in the three months prior to the study. We also excluded students who had received iron supplementation, were hypersensitive to iron preparations, experienced bleeding within the past 3 months including from worm infestations, fractures, infections, or concomitant diseases such as kidney, liver, tuberculosis, and malignancy.

Subjects’ parents provided informed consent and filled questionnaires about the state of their child’s health. Drop-out criteria were recurrent vomiting, inability to swallow the supplement according to the adjusted dosage, hypersensitivity reactions, moving out of town, quit from the study, or refused to continue the therapy. Subjects were collected by purposive sampling and underwent blood lead level measurements, pre- and post-treatment). Subjects were then given NaFeEDTA 115.4 mg (15 mg elemental iron) at a dosage of 3 mg/kgBW/day elemental iron given between meal times. Iron supplementation was given daily per oral route. If a subject vomited within less than 1 hour of taking the supplement, the iron supplement could be given at the same dose as before. But if the vomiting persisted or a subject had diarrhea as an adverse effect, that subject was considered to have dropped out of the study. The iron supplementation also had to be stopped if adverse effects such as severe gastrointestinal problems, nausea, vomiting, and diarrhea persisted. After 12 weeks of NaFeEDTA supplementation, subjects’ complete blood counts and blood lead levels were evaluated.

Subjects provided 10 mL blood specimens taken from the median cubital vein in a sterile fashion. Five mL of the blood was kept in an EDTA-anticoagulant tube for complete blood counts, at the Laboratorium Klinik Manado, and the other 5 mL was stored in a heparin tube and sent to Jakarta for blood lead level testing.

Descriptive analysis of the subjects’ characteristics was reported in distributive tables. Parametric data was used to calculate mean, standard deviation (SD), and 95% confidence interval (CI). Pretest and posttest analyses were done with paired T-test. Results were considered to be statistically significant for P values <0.05. Data were processed with SPSS for Windows version 22 software. The study was approved by the Ethics Committee of the Sam Ratulangi University Medical School, Manado.
Results

From August to November 2014, 46 children from four elementary schools were identified. After purposive sampling by physical examination and laboratory findings, 39 children met the inclusion criteria. The mean age of subjects was 8.43 (SD 0.44) years. More girls than boys had lead poisoning. Subjects' mean body weight was 24.56 (SD 3.49) kg. Anthropometric measurements showed that all subjects had good nutritional status (Table 1). Subjects' complete blood counts before supplementation showed normal levels of hemoglobin, leukocytes, and platelets according to age (Table 1).

Table 1. Subjects' characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), years</td>
<td>8.43 (0.44)</td>
</tr>
<tr>
<td>Gender, n</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
</tr>
<tr>
<td>Mean body weight (SD), kg</td>
<td>24.56 (3.49)</td>
</tr>
<tr>
<td>Mean body height (SD), cm</td>
<td>125.37 (6.46)</td>
</tr>
<tr>
<td>Mean Waterlow score (SD), %</td>
<td>99.15 (6.81)</td>
</tr>
<tr>
<td>Mean hemoglobin (SD), g/dL</td>
<td>12.96 (0.53)</td>
</tr>
<tr>
<td>Mean leucocytes (SD), cells/mm³</td>
<td>10,305 (2,332.37)</td>
</tr>
<tr>
<td>Mean platelets (SD), cells/mm³</td>
<td>337,948 (43,668.57)</td>
</tr>
</tbody>
</table>

Paired T-test revealed a significant difference in mean blood lead levels, before and after iron supplementation [36.18 (SD 11.97) vs. 5.22 (SD 2.03) μg/dL, respectively; (P<0.0001)] (Table 2).

Table 2. Serum lead levels (initial and after NaFeEDTA administration)

<table>
<thead>
<tr>
<th>Serum lead levels</th>
<th>Mean (SD), μg/dL</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>36.16 (11.97)</td>
<td>32.30 to 40.06</td>
<td>0.0001</td>
</tr>
<tr>
<td>After NaFeEDTA administration</td>
<td>5.22 (2.03)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The Talawaan District is located in the North Minahasa Regency, and consists of 11 villages. The 4 elementary schools chosen for the study were located near one and others, and isolated, thus the lead exposure were from the environment, not from vehicles. A previous study on blood lead levels in children aged 6-8 years had been done in the Talawaan District.8 Our study was conducted in a subset of children who had blood lead levels > 10 μg/dL in the previous study.

All subjects had good nutritional status, as shown by normal anthropometric parameters, in order to eliminate confounding micronutrient deficiencies that could affect the blood lead level. The US CDC showed that nutritional status is negatively related to blood lead levels in children. Good nutritional status can help prevent toxicity caused by lead.9

Subjects' hemoglobin levels were evaluated to check for anemia. Anemia is known to be an effect of lead poisoning but it may also be caused by iron deficiency, chronic disease, parasitic infection, and other conditions related to blood abnormalities. Anemia was not found in any subjects.10 Lead poisoning and iron deficiency anemia in children had been studied before, especially in high risk populations, such as in children living in lead mining areas. However, lead poisoning was found to have a greater effect on neurotoxicity than on heme synthesis.11,12

Subjects' leukocytes were evaluated to eliminate a confounding factor of infectious disease. Leukocyte levels in this study were in the normal range. Lead poisoning may increase leukocyte levels with leukocytosis occurring especially in the monocyte and neutrophil series.13

A previous study in the Talawaan District reported a high mean blood lead level of 25.8 μg/dL in children.8 We found that the mean blood lead level had increased to 36.18 μg/dL. Chronic exposure, resulting in an accumulation of lead in the bloodstream, and the tendency of increasing blood lead level as a function of age, where older children are more exposed to lead from the environment, activities, and food, may have lead to this increase only 2 years later. Chronic exposure to lead can cause high blood lead levels after a long period of time.14,15 Children are particularly prone to the effects of lead exposure.
The risk of lead exposure in villages is different from that in cities. People who live near gold mining areas are susceptible to lead poisoning over a long time frame. A gold mine is located near the Talawaan District (approximately 2 km away). Trucks transporting stones and supplies to process the gold pass through the villages, spreading lead-containing dust. Motorcycles, as main vehicle in the area, are also major contributors to the pollution problem. The villages in our study also had a similar demographic, as they are all located near a river that passes through the mining area.

Studies from 12 gold mines in Brazil showed toxicity or lead poisoning in children living nearby. The destruction of lead-rich stones and the amalgamation process in gold production, released toxic minerals including lead, which had not been water soluble prior to mining. Chronic exposure of lead-containing dust was also a cause of lead poisoning. Gold mine production resulted in unnecessary mineral residues, called tailing. The disposal of this tailing is an environmental problem, because it contains metal components, such as Pb, Hg, Zn, As, and Cd that pollutes land and water. The CDC and WHO reported on deaths caused by lead poisoning, where 97% of children living near a gold mine in Nigeria had blood lead levels of ≥45 μg/dL. However, we cannot conclude that subjects’ elevated blood lead levels in the Talawaan District are related to the presence of nearby gold mines.

In our study, 26 children had mild lead poisoning (10-40 μg/dL), 11 had moderate (40-60 μg/dL), and 2 children had severe lead poisoning (63 μg/dL and 74 μg/dL, respectively). In home visits and investigations into the potential source of pollution, no sources were found other than in their living environment.

The influence of lead poisoning in children may be minimized by improving the intake of iron and calcium. Lead competes for the same metalloprotein-binding sites as iron and calcium, thus adequate levels of these minerals may decrease the effects of lead in the body. Children with mild lead poisoning are advised to improve their nutritional intake and begin iron supplementation.

Medical therapies should be given to children manifesting symptoms of lead poisoning or children with blood lead levels ≥45 μg/dL. In our study, 7 had blood lead levels ≥45 μg/dL, hence, medical and chelating therapies, as well as iron supplementation should be given as soon as possible to decrease the blood lead levels, as recommended by the CDC. Children with severe lead poisoning should undergo complete blood screening and blood lead level evaluation weekly and then monthly. Children with manifestations of lead poisoning should be admitted to the hospital and given chelating therapy. All children with blood lead level > 20 μg/dL should be moved away from the source of lead, as recommended by the CDC. However, the situation must be discussed with the community and government.

In our study, 3 months of administration of iron in the form of NaFeEDTA, orally at a dose of 3 mg/ BW/day was adequate to significantly decrease serum lead in children with lead poisoning (P<0.0001). Furthermore, a healthy, iron-rich diet is required. NaFeEDTA was not given in conjunction with lead chelation, as chelation inhibits iron absorption. In vitro trials in rats showed a decrease in serum lead levels in the blood-brain barrier after six weeks of NaFeEDTA administration. In children with lead poisoning and iron deficiency, the administration of NaFeEDTA can decrease serum lead levels. A Bangalore study showed a decrease of serum lead levels from ≥10 μg/dL after iron fortification for six days per week for six months.

This study is the first to assess the effectiveness of NaFeEDTA administration in children with lead poisoning. Our results provide a basis for communities and health care providers to influence decision-making of the local government, as elevated serum lead levels in Talawaan children needs immediate attention. A limitation of this study was that we could not determine the precise source of lead pollution in the area, despite the suggestion of such sources by the subjects’ high lead levels which exceeded the safe threshold set by CDC. Also, our subjects did not undergo complete radiography examinations, according to CDC recommendations for evaluating children with lead poisoning, nor did they have periodic evaluations of serum lead levels, prior to initiating treatment. Medical therapy is needed in children with lead poisoning accompanied by symptoms. Recording and calculation of diet and nutrition, including all food containing iron, was also not done in this study. However, only children with good nutritional status were included in our study. In
conclusion, blood lead levels are significantly reduced after 12 weeks of NaFeEDTA supplementation in children with lead poisoning.

Conflict of Interest

None declared.

References