ATLANTIS PRESS

Advances in Health Sciences Research, volume 1

1st Public Health International Conference (PHICo 2016)

Chronic Lead Poisoning Prevention in Children with Calcium Supplementation

Sri Sofyani[1], Aznan Lelo[2]

[1]*Department of Child Health, Medical School, Universitas Sumatera Utara-Haji Adam Malik Hospital, Indonesia*
srisofyani@yahoo.com

[2]*Department of Pharmacology Medical School, Universitas Sumatera Utara, Indonesia*
aznanlelo@yahoo.com

***Abstract*— Lead poisoning is one of the environmental problems around the world affecting human health. Children are at the greatest risk because lead is more easily absorbed by their growing bodies, and because their tissues are especially sensitive to damage. Even blood lead levels as low as 5 μg/dL can irreversibly impair the development of children's brain. Lead competition with ca^{2+} in the plasma membrane transport system, binds to calmodulin and disturb the enzyme activity that causes the transcription of genes in the nervous system affected. Chronic exposure can cause behavioral disorders, reduce the level of IQ, and cause impaired growth.**

The purpose of this study is to determine the effects of calcium supplementation to decrease blood lead levels (BLLs) of children who are at high risk for chronic lead poisoning. Children aged 9-16 years who live in areas with highest traffic density in Medan (around Terminal Amplas) had chosen randomly included in this quasi-experimental study with a clinical trial design in which subjects were divided into two groups. One as control, one group received calcium with a dose of 400 mg twice daily orally for three months. Samples for BLLs were collected before and after 3 months of supplementation. Descriptive statistics were calculated at two visits (baseline, and 3 months). Potential trends in whole blood lead, and haemoglobine were assessed using paired t-tests; comparison between two treatment were assessed by unpaire t-tests. Statistical significance was defined as P < 0.05.

The highest BLLs before was 12 μg/dL, after treatment was 1.9 μg/dL; difference between means in BLLs after 3 months of follow-up was 1.327 ± 0.4346 μg/dL (P 0.004); significantly different (P< 0.05).

Calcium at dose 2 x 400 mg daily orally to children who are at high risk for chronic lead poisoning for three months can reduce BLLs significantly.

***Keywords*— children, blood lead levels, chronic lead poisoning, calcium supplementation.**

I. Introduction

Lead was one of the most dangerous environmental toxic substances. Its neurotoxic potential is highly significant but its secure blood level concentration remains unknown. Lead affects the cholinergic, dopaminergic and glutaminergic systems, thus intervening in the normal function of neurotransmision. The consequence of neurotoxicity in the central nervous system includes apoptosis and excitotoxicity. Some studies claim that cognitive decline and low IQ can occur in concentrations <10 μg/dL. Despite the fact that lead has been banned from gasoline, paint and water pipes, quite significant quantities of lead still exist, particularly in deprived areas of modern cities, in transition zones and city centers, and there are also great concentrations around lead mines and in developing countries, but even for the remaining areas there is no safe threshold. Prevention should be the single most important way of dealing with lead poisoning [32].

II. Background

Lead is a heavy metal with a bluish-grey color. It has a low melting point, is easily molded and shaped, and can be combined with other metals to form alloys. [34] For these reasons, lead has been used by humans for millennia and is widespread today in products as diverse as: pipes, storage batteries, pigments and paints, glazes, vinyl products, weights, shot and ammunition, and radiation shielding [33]. Because of increasing human activity, the level of lead in the biosphere has risen in the past 300 years [26]. Lead can get into the environment and human body and make someone be exposures. Sources of lead poisoning can include emissions from vehicles using leaded petrol and from base metal mining, smelting or lead manufacturing or recycling industries, dust, soil, paint, toys, jewelry, drinking water, candies, ceramics, folk medicine and cosmetics (DHOCNY, 2007). The following are the pathways (means by which) lead poisoning can occur; ingestion (eating or accidentally swallowing), inhalation (breathing in), skin absorption, or via the placenta of a mother who herself is lead-poisoned. Lead enters the human body when people breathe, eat, swallow or drink any substance that contains lead. Water is contaminated when it flows through a pipe or brass fixture that contains lead (DHOCNY 2007). Lead-based paint usually has a sweet taste that appeals to children to swallow or put in their mouth. More over, lead from fuel can contaminate soil, and increase the blood level of children in urban areas [8], as a result of contact with the soil.

Lead poisoning is one of the environmental problems for people living in urban area. Lead can cause serious illness for young people, especially to brain development. It can reduce the level of IQ cause impaired growth and harm kidneys. Severe poisoning can induce coma, or cause death [33]. Ancient Egyptian and Greek physicians recognized lead poisoning 5000 years ago. It is considered as one of the oldest diseases in human history [11]. Then, lead poisoning has been recognized as a serious environmental health problem throughout the world, particularly, for poor children in developing country [25]. In recent years the focus in lead poisoning has shifted away from adults exposed to high doses in industrial settings to the larger population of asymptomatic children with lesser exposures.

In Indonesia, children who live in urban areas with higher traffic density have a higher risk of lead poisoning. “Our data indicate that Indonesian children living in urban area are at increased risk for blood lead levels above the actual acceptable limit” [17]. The increasing number of industries in Indonesia has been associated with rising heavy metal pollution in several areas, such as in Jakarta, Dumai and Medan [2], [3], [21], [15].

Research conducted in the city of Medan, found that there is an apparent link between the increase of the intensity of a motor vehicle with the air lead levels in the city of Medan. Air lead levels is highest in Terminal Amplas, i.e. 32.67 ug/m3, then in Pinang Baris and at Jalan Brigjend Katamso at the time of observation from 13.00 - 14.00 is 23 ug /m3 [16]. While the air lead level threshold based on Government Regulation (PP) 41 of 1999 on air pollution control is 2 ug/m3, this indicates that the air lead levels far above the city of Medan threshold value [10].

The definition of an elevated concentration of lead in the blood according to the Centers for Disease Control and Prevention (CDC 1991) is 10 ug/dl. However, evidence indicating that some health effects can occur below this threshold is accumulating. Recent analyses suggest that health effects may become apparent at concentrations of <5 μg/dl and, indeed, that no evidence exists for a threshold, even at 1 μg/dl (Schwartz 1994). For the purpose of this study, the concentration of blood-lead incurring the lowest population risk was considered to be 0-1 μg/dl, in the absence of scientific consensus and pending further investigation. The measurement of blood-lead concentration in preindustrial humans has shown that the contribution of natural sources of lead to human exposure is small; Flegal and Smith (1992) have estimated that pre-industrial humans had blood-lead concentrations of only 0,016 μg/dl.

We have done a cross-sectional study as a preliminary study; on sample of this elementary private school children Al-Wasliyah Timbang Deli, Medan last year, obtained their mean blood lead levels was 2.580 μg/dl (lowest blood lead levels of 1.477 μg/dl and the highest 3.989 μg/dl, the median 2.735 μg/dl). In this study the Child Behavior Checklist [1] was completed by parents for each participating child. These 118-item measures assess the frequency of a range of behavioral and psychopathological symptoms in children, yielding subscale scores for internalizing and externalizing problems, and a total behavior problem score.

And the result was very surprising; it was found that the number of children that the levels of their blood lead above the mean value was 54 percent. Of this group there were 33.3 % have delinquent problem, 11.1 % have aggressive behavior, 40.7 % have social problems, 29.6 percent have somatic problems, 22 percent suffered from impaired withdrawn; 7.4 percent had depression, and 7.4 percent had attention problems (there was a child who had some behavioral problems at once). From this preliminary investigation it was found that blood lead levels affect internal and external behavioral disorders of children (OR 4.5 for internal behavioral disorders and OR 5.3 for external behavioral disorders). Based on these results (result have not publish yet) it is necessary to find the good management to prevent the occurrence of behavioral disorders in children with blood lead levels were relatively high in the area of pollutants in the city of Medan.

From several previous studies it is known that calcium is one ingredient that can lower blood lead level [14], [24], [4], [30] the result are different, some did not find any significant reduction.

Because of prevention should be the single most important way of dealing with lead poisoning [32], we have done a study to test our hypothesis that supplementation with calcium 2 x 400 mg/day for 3 months at primary school age children can lower blood lead level significantly.

III. Methodology

This quasi-experimental design of randomized clinical trial was conducted in school children (aged 9 – 12 years old). The study subjects were at high risk of lead pollution in the city of Medan, whom is domiciled and doing activities (school) in overcrowded vehicles. The exclusion criteria were children with kidney failure, abnormalities of brain dysfunction, malnutrition, history of allergies or resigned after being given an explanation.

Subjects were divided into two groups by using simple random sampling; one group as control (n = 26) and another group (n = 30) were treated by giving calcium supplements at a dose of 2 x 400 mg daily for 3 months. Venous blood was collected from each child using vacutainer as much as ± 6 cc, before and after 3 month of treatment. The content of lead in blood (mg/dL) was measured in duplicate samples by atomic absorption spectrophotometry (AAS) using a Perkin-Elmer spectrophotometer. A coefficient of variation <5% was reached before analysis of actual samples.

The study was conducted in Private Elementary Schools Al-Wasliyah Timbang Deli, Jalan Pertahanan, District Medan Amplas, Medan, Province of Sumatera Utara. Assent was obtained from the participated subjects with consent from their parents/guardians. The study was conducted after obtaining approval from the Health Research Ethical Committee of Medical School, University of Sumatera Utara.

Descriptive statistics were calculated for the total sample at two visits (baseline, and 3 months). Means, standard deviations, and medians and ranges were used to summarize continuous variables, and proportions for categorical variables. Potential trends in whole blood lead, and hemoglobin over time were assessed using un-paired Student's t-tests. While comparison between two treatment were assessed by unpaired Student's t-tests. Statistical significance was defined as P value < 0.05.

IV. Result

A total of 62 children were enrolled; 32 in Ca supplementation group and 26 as control without calcium. Of this, 56 completed 3 months of follow up (30 and 26 respectively). Subjects who did not complete the study did not return as per schedule requirements. Compliance with supplement administration was 82 ± 18% for Ca group. Mean and SD blood lead level data at enrolment are 3.053 and 2.676. There were no statistically significant differences between the group at enrolment on age, sex, family income, nutrition status, measures of home exposure, and hand/object-to-mouth behaviour.

TABLE 1
Base line characteristics Variables at enrolment (±SD)

Variable	**Control Group**	**Ca Group**
Age (y)	10.7 ± 1.3	10.5 ± 1.7
Family income (Rp)	2.035.000 ± 263.000	2.035.000 ± 115.000
Hand/object to mouth (touches/min)	0.4 ± 0.6	0.4 ± 0.5

TABLE II
Biochemical Mean Values During the Course of the Study

Variables	**Control**	**Calcium**	**Significancy**
BLLs (µg/dL) **Enrolment**	2.538 ± 0.07807	3.053 ± 0.4886	NS
BLLs (µg/dL) **3 Months**	2.462 ± 0.1269	0.1983±0.09428	= 0.0001
Significancy	0.6096 (NS)	<0.0001	
Haemoglobin (g/dL) **Enrolment**	12.98 ± 0.9978	12.76 ± 0.586	NS

Table II shows that the percentage reduction of blood lead level in calcium group was 93.6%, while in control group was 3%. This different is highly significant (P = 0,000).

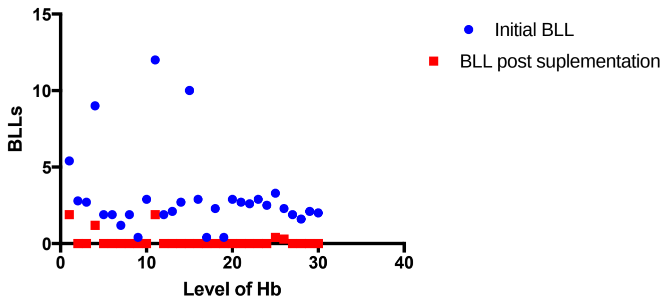

Fig. 1 The Level of Haemoglobin, Blood Lead Level at Enrolment and After Treated.

There were no serious adverse events. No abdominal pain complaints occurred in both groups.

V. DISCUSSION

There is an abundance of evidence, which demonstrates that dietary calcium decreases gastrointestinal lead absorption and thereby reduce lead toxicity. Considerable experimental data support the premise of potential role for Ca supplementation in the amelioration of Pb poisoning. Ca-binding proteins have a high affinity for Pb. ([5] in rodent studies, BLL in exposed animals are higher in those fed Ca deficient diets. [13] Studies using stable isotopes of Pb fed simultaneously with Ca to adults showed a decreased in Pb absorption. [6] Increasing dietary Ca is associated with decreases in gastrointestinal lead absorption and BLL in some studies [35]; [20], [22], [7], [27] but not in others. [28], [19] In a longitudinal study Lanphear et al found a marginal correlation between BLL and Ca intake in a cohort of 12- to 24-month old children who received 900 mg Ca per day.

Furthermore, an interventional study aimed at preventing lead accumulation in infants in which formula-fed non led poisoned infants were supplemented with Ca glycerophosphate (188 mg/L vs. 465 mg/L) did not find a benefit over 9 months of treatment. [30] BLL increased 2.4 µg/dL in the unsupplemented and 2 µg/dL in the supplemented group. Of interest, there was no effect of supplementation on urinary Ca excretion or iron status [30]. The published data supporting a potential role of Ca supplementation in the treatment of mildly to moderately lead poisoned children are limited. A single uncontrolled study examined the potential effects of Ca-supplementation on a Ca-deficient and Lead poisoned population in China. The source of Lead exposure in this group was from leaded gasoline usage and industrial pollution. Shen et al provided a total daily intake 0f 800 mg Ca (the current recommended dietary allowance for this age group) to a group of 35 children who were aged 49 to 70 months and whose pre-treatment Ca intake was 300 mg/day. A 10 µg/dL fall in BLL was observed over a 2 months period, although lead exposure was presumably ongoing and changed [31].

In our study using 800 mg/day Calcium supplementation, we found 2.855± 0.4976 µg/dL difference between means (reduction 93.6%) in BLLs after 3 months of follow-up Ca supplemented children and un-supplemented control subjects, P value <0.000, significantly different (P, 0.05). This formed the basis of our power calculation. A total of 800 mg supplementation was also a level unlikely to be associated with toxicity.

There is increasing interest in the interaction of nutritional deficiencies with toxic metals. Iron deficiency and elevated blood lead concentrations (PbB) reportedly occur together, and zinc also plays an important role in lead metabolism. After controlling for initial BLLs, groups administered zinc and/or iron did not have lower BLLs concentrations than the placebo group ($P < 0.05$). Neither iron nor zinc can be recommended as the sole treatment for lead-exposed school children [29]. From this study we also find that is no correlation between blood lead levels with blood haemoglobin levels. See fig.1

Physiologically Ca level is determined by the levels of vitamin D in the blood. The relationship of serum vitamin D and whole-blood lead is possibly influenced by growth and/or calcium homeostasis in some children and adults. Low dietary intake of vitamin D and calcium are known risk factors for high bone lead levels. Optimal vitamin D status is known to have beneficial health effects and vitamin D supplements are commonly used. It has been suggested that vitamin D supplementation may increase blood lead in children and adults with previous lead exposure. In fact, high-dose vitamin D3 supplementation and the concomitant increased serum 25D did not result in increased whole-blood lead concentration [12].

Previous studies on animals have revealed that garlic (Allium sativum) is effective in reducing blood and tissue lead concentrations. The frequency of side effects was significantly (p=0.023) higher in d-penicillamine than in the garlic group. Thus, garlic seems safer clinically and as effective as d-penicillamine. Therefore, garlic can be recommended for the treatment of mild-to-moderate lead poisoning [18]. However garlic may trigger abdominal discomfort and make our body smelled bad

V. Conclusions

We conclude that Ca supplementation 800 mg/day is effective for the treatment of children who are 9 to 12 years of age, have blood lead level between 0,4 and 12 μg/dL.

Acknowledgment

This study was supported by a grant from Universitas Sumatera Utara.

References

[1] Achenbach, T. M. *Manual for the Child Behavior Checklist/4-18 and 1991 profile*. Burlington, VT: University of Vermont, Department of Psychiatry.

[2] Amin B. *Akumulasi dan distribusi logam berat Pb dan Cu pada Mangrove (Avicennia marina) di perairan pantai Dumai, Riau* [Translation: Accumulation and distribution of heavy metal Pb and Cu on Mangrove (Avicennia marina) in coastal Dumai Riau] IN INDONESIAN] University of Riau Indonesia 2001 http://www.unriac.id/jurnal/jurnal_natur/vol4(1)Bintal.pdf

[3] Anggarini, D. *Analysis of heavy metal Pb, Cd, Cu and Zn in a seawater, sedimen and Geloinacoaxans in coastal Dumai, Riau*. 2007 http://www.images.cientherell4.multiply.multiplycontent.com.journal/item/1

[4] Ballew C, Khan LK, Kaufmann R, Mokdad A, Miller DT, Guntert EW. *Blood lead concentration and children's anthropometric dimensions in the Third National Health and Nutrition Examination Surveys*. J Pediatr.1999;134:623-30

[5] Simons TJB. *Cellular interactions between lead and calcium. Br Med Bull.*1986;42 :431– 434

[6] Blake KCH, Barbezat GO, Mann M. *Effect of dietary constituents on the gastrointestinal absorption of 203Pb in Man*. Environ Res.1983;30 :182– 187

[7] Bogden JD, Gertnaer SB, Christkos S, Kemp FW, Yang Z, Datz SR, Chu C. *Dietary calcium modifies concentrations of lead and other metals and renal calbindin in rats*. J Nutr.1992;122 :1351– 1360

[8] CHW & HCHN (The Children's Hospital at Westmead (CHW) & Kaleidoscope, Hunter Children's Health Network (HCN). *Fact sheet: Lead, Kids Health, The Children's Hospital at Westmead & Kaleidoscope, Hunter Children's Health network*. 2008 http://www.chw.edu.au/parents/kidshealth/safety_factsheets/pdf/lead.pdf

[9] Fullmer CS, Edelstein S, Wasserman Rh. *Lead-binding properties of intestinal calcium-binding proteins*. J Biol Chem.1985;260 :6816–6819

[10] Girsang, E. *Hubungan kadar timbal di udara ambien dengan timbal darah pada pegawai dinas perhubungan terminal antar kota Medan, Tesis Paska Sarjana Universitas Sumatera Utara*. 2008; 36-52

[11] Graef JW. *Foreword in getting the lead out the complete resource on how to prevent and cope with lead poisoning*. Kessel and O'Connor Plenum Trade, New York, 1997 http://www.questia.com/library/book/getting-the-lead-out-complete-resource-on-how-to-prevent-and-cope-with-lead-poisoning-by-irene-kessel-john-t-oconnor.jsp [ONLINE BOOK]

[12] Groleau V, Herold RA, Schall JI, Wagner JL, Dougherty KA, Zemel BS, Rutstein RM, Stallings VA. *Blood lead concentration is not altered by high-dose vitamin D supplementation in children and young adults with HIV.* J Pediatr Gastroenterol Nutr. 2013 Mar;56(3):316-9.

[13] Han S, Pfizenmaier DH, Garcia E. *Effects of lead exposure before pregnancy and dietary calcium during pregnancy on fetal development and lead accumulation*. Environ Health Perspect.2000;108 :527– 531

[14] Haryanto, B. *Pengaruh suplemen kalsium terhadap penurunan kadar timah hitam dalam darah (studi komunitas siswa Sekolah Dasar di kota Timah Bandung)*, disertasi program doctor, Program Pascasarjana Fakultas Kesehatan Masyarakat, Universitas Indonesia, Jakarta. 2008:90-91

[15] Hasan W. *Pencegahan keracunan timbal kronis pada pekerja dewasa dengan suplemen kalsium.* Makara, Kesehatan, Vol 16, No1 , Juni 2012:1-8

[16] Sitohang R. *Pengaruh intensitas kendaran bermotor terhadap emisi logam timbal ke dalam udara ambien di kota Medan* [Thesis} Indonesia; Universitas sumatera Utara; 2001

[17] Heinze . *Assessment of lead exposure in school children from Jakarta* http://ehp.niehs,nih.gov.members/1998/106p499-501heinze/heize-full.html

[18] Kianoush S, Balali-Mood M, Mousavi SR, Moradi V, Sadeghi M, Dadpour B, et al. *Comparison of therapeutic effects of garlic and d-Penicillamine in patients with chronic occupational lead poisoning.* Basic Clin Pharmacol Toxicol. 2012 May;110(5):476-81

[19] Lanphear BP, Hornung R, Ho M, Howard C, Eberle S, Knauf K. *Environmental lead exposure during early childhood*. J Pediatr.2002;140 :40– 47

[20] Lederer LG, Franklin CB. *Effect of calcium and phosphorus on retention of lead by growing organisms*. *JAMA*.1940;114 :2457– 2461

[21] Lestari and Edward. *Dampak pencemaran logam berat terhadap kualitas air laut dan sumberdaya perikanan (Studi kasus kematian massal ikan-ikan di Teluk Jakarta)* [TRANSLATION: Effect of heavy metals pollution to seawater quality and fishery resource (case study on fish death in Jakarta Bay)] {IN INDONESIAN{ Makara, Sains, Vol 8, No.2, Agustus 2004: 52-58 http://journal.ui.ac.id/upload/artikel/02_Dampak%20Pencemaran%20logam%20Berat_Lestari.PDF

[22] Mahaffey KR, Gartside PS, Glueck CJ. *Blood lead levels and dietary calcium intake in 1- to 11-year-old children: the Second National Health and Nutrition Examination Survey, 1976 to 1980*. Pediatrics.1986;78 :257– 262

[23] Kianoush S, Balali-Mood M, Mousavi SR, Moradi V, Sadeghi M, Dadpour B,et al. *Comparison of therapeutic effects of garlic and d-Penicillamine in patients with chronic occupational lead poisoning.* Basic Clin Pharmacol Toxicol. 2012 May;110(5):476-81

[24] Markowitz, ME., Sinnet, M and Rosen, JF. *Randomized trial of calcium supplementation for childhood lead poisoning*. Pediatrics.2004;113,1:e34-e39.

[25] Meyer, Pamela A.; Mc Geehin, Michael A., Falk, Henry. *A global approach to childhood lead poisoning prevention*. Int J Hygiene Envi Health, 2003, p 206, 363-369.

[26] NHMRC (National Health & Medical Research Council) *NHMRC Public Statement, August 2009, Blood lead levels: Lead exposure and health effects in Australia*. National Health & Medical Research Council, http://www.nhmrc.gov.au/filed_nhmrc/file/publication/synopses/gp03-lead-pub-stmt.pdf

[27] Quarterman J, Morrison JN, Humphries WR. *The influence of high dietary calcium and phosphate on lead uptake and release*. Environ Res.1978;17 :60– 67

[28] Rosen JF, Chesney RW, Hamstra A, DeLuca HF, Mahaffey KR. *Reduction in 1, 25-dihydroxyvitamin D in children with increased lead absorption*. N Engl J Med.1980;302 :1128– 1131

[29] Rosado JL, López P, Kordas K, García-Vargas G, Ronquillo D, Alatorre J, et al. *Iron and/or zinc supplementation did not reduce blood lead concentrations in children in a randomized, placebo-controlled trial*. J Nutr. 2006 Sep;136(9):2378-83.

[30] Sargent JD, Dalton M, O'Connor G, Olmstead E, Klein RZ. *Randomized trial of calcium glycerophosphate-supplemented infant formula to prevent lead absorption.* Am J Clin Nutr.1999;69 :1224–1230

[31] Shen XM, Guo D, Zhou J, Chonghuai Y. *Intervening role of calcium on lead toxicity in children: experimental study and clinical verification.* Chinese J Child Health.1993;1 :157

[32] Vorvolakos T, Arseniou S, Samakouri M. *There is no safe threshold for lead exposure: A literature review*. Psychiatry. 2016 Jul-Sep;27(3):204-214.

[33] WHO HECA (World Health Organization Healthy Environments for Children Alliance) 2002 (a) *Issues brief series: Lead* www.who.int/heca/informaterials/lead.pdf

[34] WHO. *Childhood Lead Poisoning*. WHO.2010

[35] Ziegler EE, Edwards BB, Jensen RL, Mahaffey KR, Fomon SJ. *Absorption and retention of lead by infants*. Pediatr Res.1978;12 :29–34