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by Irfannuddin Irfannuddin

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The effect of high aluminium water consumption on parameters of neuron, blood and renal function

Irfannuddin Irfannuddin[1*], **Milla Bustan**[2], **Ummi Maktum**[3], **Ratika Febriani**[2], **Yakub Rahadiyanto**[1]

[1] Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[2] Faculty of Medicine, University of Muhammadiyah Palembang, Palembang, Indonesia
[3] Nursing Academy of Pangkal Pinang, Bangka, Indonesia

E-mail : irfan.md@unsri.ac.id

Abstract. Mining process causes contamination of Aluminium in drinking water consumed by Bangka Island residents. The study was conducted to identify the influence of high aluminium water consumption on serum aluminium level, serum brain derived neurotrophic factor (BDNF), serum ferritin, blood haemoglobin (Hb), and urine albumin to creatinine ratio (UACR). Men aged 26-45 years old were allocated into two groups. The first group was subjects who have consumed well water for at least 5 years. Aluminium levels in well water were sampled from seven wells and the average levels were higher than threshold. The control group was subjects who have consumed tap water for at least 5 years. The average level of aluminium in the tap water from seven houses was still within the normal limit. Serum aluminium levels of men who consumed high aluminium containing water were significantly higher than control group. Men who consumed high aluminium water had significantly lower levels of BDNF and ferritin, and were also associated with lower Hb levels. Both groups had no difference in UACR and were still within normal limits. High aluminium water consumption may have an impact to decrease the indicators of cognitive and blood functions, but has no effect on renal functions.

1. Introduction

Aluminium is a heavy metal that abounds in the Earth's crust [1]. The mining industry causes aluminium from within the Earth's crust to be exposed to the surface thus polluting soil, water, air, and food crops [2]. Aluminium is absorbed into the body through the digestive tract [3]. Aluminium exposure is thought to be associated with cognitive degeneration, iron deficiency anemia, osteomalacia and decreased renal function [4]. Bangka is a small province in Indonesia with a population of 1.3 million people. Bangka is an island with the largest tin mining area [5]. However, the province was ranked first for the prevalence of disease which is associated with kidney and hypertension, and the 10th rank for the prevalence of emotional mental disorders in Indonesia. In addition, the province has an anemic prevalence higher than the Indonesian average [6,7].

The clinical effects of aluminium exposure occur over the long term, but in the long process there have been physiological changes that can be detected through laboratory indicators. Research needs to be done to explore whether exposure to aluminium has had an impact on changes in laboratory indicators in productive age groups who have not experienced clinical disorders due to aluminium, for early prevention efforts. This study was conducted to identify the effect of water consumption exposure with high aluminium content on serum aluminium levels, serum Brain Derived Neurotrophic Factor (BDNF) as an indicator of neuron functions. Hematologic indicators were identified by

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measuring serum levels of ferritin and haemoglobin (Hb), and measurement of urine albumin to creatinine ratio (UACR) to assess renal function.

2. Methods

All study protocols have been reviewed and approved by the Health Research Review Committee, Faculty of Medicine, Universitas Sriwijaya. Ethical approval certificate number 50/kepkrsmhfkunsri/2017. A quota sampling was conducted on two groups of societies. The first group is 39 male, aged 26-45 years, who live in a villager disrict of "Labu Air Pandan ", Bangka Island. They all have been consuming well water for at least 5 years. Subjects were selected by systematic random sampling. Al content in water was measured from seven wells in the village, and the mean Al level was 0.49 ± 0.14 mg/L, higher than maximum threshold listed by World Health Organization (WHO) (0.2 mg / L) [8]. As a control group, subjects of 38 adult male, aged 26-45 years, were selected consecutively. They all live in "Pangkal Pinang" city, Bangka Island, and have consumed tap water for at least 5 years. Detection of aluminium content was performed on tap water of seven houses selected consecutively in the city, and obtained an average aluminium level of 0.12 ± 0.7 mg/L, which is still below the WHO threshold.

2.1. Drinking water collection

Well water samples were taken in the morning before being used for daily living purposes. Well water was taken on the top surface. For tap water, the tap was let to flush for 15 minutes before water was collected. Water was collected in polypropylene bottles. Before collecting water, bottles were soaked in 5% nitric acid for 48 hours and rinsed repeatedly with ultra-pure water. Two ml of 69-70% nitric acid was added to water for preservation. Samples were stored at 4oC until laboratory analysis.

2.2. Blood and urine samples

The subjects have agreed to participate in the study by signing informed consent. Subjects filled out questionnaires for self-data before blood and urine samples were taken. Blood samples were obtained from the cubital vein of subjects in the resting condition in the morning. Blood of about 5 ml was taken with disposable syringe. For Hb analysis, 1 ml of blood was fed into a polypropylene tube containing EDTA solution. For serum (Aluminium, ferritin, and BDNF) examination, 4 ml of blood was then inserted into micro tube and then centrifuged 3000 rpm for 20 minutes in order to get the supernatant layer. The tube is labelled for respondent code, then was inserted into a blood carrier with temperature 2-4oC. Urine samples in both groups were taken in the morning with polypropylene bottles. Urine was then inserted to micro tube and centrifuged 3000 rpm for 20 minutes to take the supernatant. The blood and urine samples were stored temporarily, at -80'C in local laboratory. Once collected, all samples were flown for 45 minutes to Palembang, South Sumatra in 2-4oC sample carrier for analysis.

2.3. Laboratory analysis

Water and serum aluminium, serum ferritin, blood Hb, and UACR were analyzed in Laboratory of the Ministry of Health, South Sumatra. Aluminium levels of serum and water were analyzed by the same method. Water/serum aluminium levels were measured by a fully automatic atomic absorption spectrometers methods using Shimadzu AA-6300. Standard addition method was initially conducted before automatic analysis following manual of Shimadzu News 3/2003. Serum ferritin levels was determined by automated quantitative enzyme linked fluorescent assay performed by mini VIDAS Ferritin instruments.

Table 1. Age and aluminium level of both groups.

	Drink water contains high Aluminium (n=39)	Drink water contains low Aluminium (n=38)	P
Age (years)	35.7±5.2	36.0±5.7	0.790[a]
Aluminium serum (µg/L)	26,58±9.28	21,14±9.54	< 0.05[a]

[a]Independent T test

Blood Haemoglobin levels were measured by automated cell counting Sysmex XT 2000i. Levels of albumin and creatinine was measured with automatic quantitative spectrophotometer using Bio systems S.A reagents. A sandwich enzyme-linked immunosorbent assay (ELISA) with Human BDNF ELISA kit, Sunlong Biotech was conducted to measure BDNF serum level, in Molecular Biology Laboratory in Faculty of Medicine Sriwijaya University. ELISA procedure were following manual instruction. Standard curve was plotted as optical density (OD) 450nm in each standard solution compared with standard solution concentration. The concentration of human BDNF samples were interpolated from standard curve. Laboratory personnel were blinded to the identity of the specimens.

2.4. Statistical analysis
Data were analyzed with SPSS Software version 16.0. Comparative analysis of numerical values used independent T test and Mann-Whitney U Test, and Chi-square test was used to compare proportional values of two groups. Medicalc software was used to calculate the relative risk.

3. Result
Both groups had no difference in age, and all were within the productive category age group (Table 1). Serum aluminium levels of people who consumed water high aluminium-content were significantly higher than control group. It should be noted that, serum aluminium levels in both group were above the reference threshold of commercial laboratories (10 µg/L) and well above the US Department of Health, and The Scientific Committee on Health Environmental and Emerging Risks (SCHEER) European Commission recommendation of 1-3 µg/L[8,9].

Tabel 2. Laboratory indicators between groups.

	Drink water contains high Aluminium (n=39)	Drink water contains low Aluminium (n=38)	P
BDNF serum (pg/mL)	59.93 (24.92-99.31)	129.31 (28.68 – 391.18)	< 0.01[b]
Ferritin serum (µg/L)	94.91 (2.83 – 190.12)	153.99 (13.37-503.55)	< 0.001[b]
Haemoglobin (g/dL)	14.09±1.24	15.18±1.13	< 0.001[a]
UACR (mg/g)	3.30 (1.60-13.10)	4.65 (0.10-18.30)	0.227[a]

[a] Independent T test; [b] Mann-Whitney U test

Table 3. Proportion of lower haemoglobin levels.

	Haemoglobin levels		P
	< 13.0 g/dL	≥ 13.0 g/dL	
	n(%)	n(%)	
Drink Higher Aluminium	9 (23.1)	30 (76.9)	
Drink Lower Aluminium	0 (0)	38 (100)	<0.01*
Total	9(11.7)	68 (88.3)	

*Chi square test
RR= 18.53; 95%CI (1.12 – 307.53), p < 0.05

Table 4. Proportion of UACR ratio.

	UACR Ratio	
	< 30 mg/g	≥ 30 mg/g
	n(%)	n(%)
Drink Higher Aluminium	0 (0)	39 (100)
Drink Lower Aluminium	0 (0)	38 (100)
Total	0(0)	77 (100)

Table 2 shows that the subjects who consumed water containing high aluminium, had significantly lower levels of BDNF than the control group. Their ferritin and Hb levels were lower than the control group, and there was no differences on UACR. The analysis was continued to assess the proportion of

subjects with the level of Hb below 13.0 g / dL, the level which is categorized to iron deficiency anaemia based on guidelines of Ministry of Health, Republic of Indonesia[6]. Table 3 shows that high water consumption of aluminium had an effect on low Hb content. For renal function, UACR results between the two groups was not different, and all of them still had normal levels, below 30 mg/g (see Table 4).

4. Discussion

Serum aluminium levels were found to be higher in the high aluminium water consumption group. Exposure to aluminium through drinking water has a direct impact on elevated levels of aluminium in the blood. Aluminium pollution in the water supply has caused many diseases to the inhabitants of Camelford, England [10]. Aluminium enters the body through drinking water and will be absorbed via gastrointestinal in the range 0.1-0.6% [11]. The fact of concern of this study is that although the control group had lower levels of aluminium, their serum aluminium levels remained higher than normal thresholds. This suggests that low aluminium water consumption did not reduce the risk of aluminium entry into the blood of the inhabitants. Aluminium enters the body not only from the consumption of drinking water, but also from other sources. Aluminium can be contained in vegetables and animal tissues absorbed from soil and water [4]. Aluminium is also consumed in the form of drugs. Aluminium-containing compounds are widely sold freely in the form of cosmetics, deodorants and over the counter (OTC) drugs such as antacids [12]. Aluminium can also be absorbed through inhalation and skin contact [3]. Ceramic glazing workers who exposed to aluminium through inhalation and oral, had higher serum aluminium levels than controls [13].

Aluminium is one of the most abundant metals in the earth. This metal is found in most rocks in the form of alum inosilicates. Aluminium can also evaporate into air emissions, in mining wastewater, and absorbed in plants. Aluminium spreads into the ecosystem through weathering and rock fragmentation [11]. Bangka Island is an island that became one of the massive tin mining sites. Mining can mobilize aluminium from the soil and rock, exposing it to the surface, polluting the soil, water, air, and food crops. The metal content of water extracted from the former tin mine in Bangka had exceeded the pollution quality standard. The saturation of aluminium in the soil in Bangka was relatively high, i.e.> 60%, with a low pH level of 4.87.17 The extent of aluminium absorption depends on pH. The low pH will increase the mobilization of aluminium from land to water environment [14].

Aluminium also still contained in the tap water. Aluminium is a substance added during the water purification process in the form of alum. Aluminium acts as a clot of solids that dissolve in water [15]. Al is widely used as coagulants to minimize the filtration membrane fouling in the pre-treatment of water supply. Farizwana et al revealed that aluminium content was high enough in tap water from private drinking water companies in the Johor region of Malaysia, which is $0.99 \pm 1.52\mu g / L$ that exceeds WHO threshold [16].

Heavy metals that enter the body will be distributed according to their affinity. Once absorbed, aluminium accumulates in the bones, brain, liver and kidneys. Some heavy metal ions are the prosthetic group of oxygenase enzymes that play a role in the oxidation-reduction process. In high concentrations, heavy metals are toxic to cells, because they act as oxidants and bind to organic molecules such as DNA and proteins, and damage the structure of DNA and proteins [17]. This study has proved that BDNF levels of high water consumption group of aluminium were lower than controls. Aluminium has been detected as a significant risk factor for spurring the inflammatory process that affects the degeneration of neuron cells [18]. Research on animals fed aluminium has proven that aluminium passed through the Blood Brain Barrier (BBB) and enters the brain cells [19]. Gradually, aluminium accumulates in brain tissue and cannot be eliminated, and causes lesions that are similar to Alzheimer's disease (AD) lesions [19,20]. Aluminium interferes with the iron homeostasis and stimulates peroxidation of membrane lipids, on the other hand, aluminium also interferes with calcium homeostasis. Those will increase free radical and cause oxidative stress. Disturbance of Ca homeostasis will lead to depletion of BDNF and others neurotrophic factors, and stimulate Tau phosphorylation, which affects neurofibrillary tangles [15,21].

This study has shown that consumption of high aluminium-containing water has an impact on low ferritin levels, and is at risk of lowering Hb levels. A study showed that the mean haemoglobin values in the Aluminium tile factory worker group were lower than the control group, and resulted in anaemia

[13]. In some animal experiments, exposure to aluminium consumption has an impact on the decrease in Hb, Haematocrit, serum Fe and the amount of RBC [22–24]. Al reduces iron absorption in the digestive system [25]. In the blood, aluminium competes with Fe to bind transferrin [26,27]. The affinity between transferrin to aluminium, and transferrin to Fe is always constant, so, if there is an increase in Al content, more transferrin will be bound to aluminium than Fe [28]. This will lead to a decrease in Fe transport. Aluminium also affects inhibiting erythropoiesis by reducing heme synthesis and globulin to form haemoglobin in bone marrow [25,26]. Metabolic iron disorders have a direct impact on the decrease in ferritin levels. Ferritin is an intracellular protein that plays a role in iron atoms. Ferritin is synthesized when the body needs atomic iron storage. The decrease in iron deposits is reflected by low serum ferritin levels [29].

This study did not prove that high aluminium consumption and elevated serum aluminium level increased the UACR ratio. As part of heavy metal, aluminium is thought to damage the kidney tissue. The consumption of aluminium chloride for 21 days has an effect on the degeneration and inflammation process in albino rats' kidney tissue [30]. However, scientific proof of renal damage due to aluminium, is still not convincing. The aluminium content in serum had no correlation with renal function variables in Saudi school children [31]. Aluminium accumulation, will only affect the metabolism of kidney cells and cause oxidative stress when accompanied by low water intake. However, and the condition was not accompanied by a significant decrease in function.36 Injection of aluminium hydroxide for 6 months, had raised serum aluminium levels, but not significantly reduced renal function [14]. Long-term aluminium retention has not been shown to lead to early decline of renal function. The risk of toxication aluminium actually occurs in patients with renal failure who administered haemodialysis. Aluminium accumulation occurs because dialysis fluids containing aluminium, and consumption of high doses of Al to balance the body's phosphate levels. These conditions are at risk for disrupting bone and neuron function [11].

5. Conclusions
High aluminium water consumption may have an impact to decrease the indicators of cognitive and blood functions, but has no effect on renal functions. Data that need to be considered from this study are subjects who drink water content low aluminium also have high levels of Al in their blood. Further research is needed to reveal various sources of Al pollution on the islanders of Bangka.

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