Iodine supplementation into drinking water improved intelligence of preschool-children aged 25-59 months in Ngargoyoso sub-district, Central Java, Indonesia: A randomized control trial

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Abstract

To date there is no iodine supplementation trial in relation to intelligence of the preschool children aged 25-59 months reported. Therefore, the aim of the study was to test hypothesis whether iodine supplementation presented in "*kendi*" (water-pitcher) can increase urinary iodine excretion and the intelligence quotients of preschool children aged 25-59 months. A randomized, placebo, controlled trial was conducted in Ngargoyoso sub-district, Central Java, Indonesia. Sixty-seven preschool children aged 25-59 months with urinary iodine excretion <100µg/L were allocated randomly into two groups. The treatment group received 100µg iodine/day and the control group received placebo for twelve weeks. Urinary iodine excretion was measured by using method A (Sandell-Kolthoff reaction) at an accredited laboratory for iodine measurement. Intelligence scores were measured by using Stanford-Binet Scale. Basal and post-treatment data on urinary iodine excretion and intelligence scores were then compared and analyzed using Student's *t* test. Statistically, urinary iodine excretion significantly increased from 62.45 (±26.21) µg/L to 244.55 (±120.19) µg/L and from 71.15 (±22.32) µg/L to 120.00 (±79.77) µg/L in the treatment and placebo groups, respectively. Comparison between groups revealed significant difference ($p<0.001$). Intelligence scores in the treatment group increased significantly from 101.48 (±11.03) points to 110.27 (±9.40) points, while in the control group there was a decrease from 105.18 (±9.62) points to 103.06 (±9.99) points. Iodine supplementation (100µg/day) within 12 weeks increases intelligence scores by 8.8 points.

Keywords: ***iodine supplementation, preschool-children, urinary-iodine- excretion, intelligence scores, kendi.***

1. Introduction

Iodine Deficiency Disorders (IDD) is a public health problem in Indonesia (Djokomoeljanto et al, 2004) including some mountainous areas of Central Java. Last survey showed a substantial increase of total goiter rate (TGR) from 9.8% in 1998 to 11.1% in 2003 (Atmarita, 2005). About 54 million people in Indonesia are living in iodine deficient area, with cretins estimated 9,000/year (MoH, 2000). However, cretinism is just the tip of the ice-berg; many more are sub-clinically hypothyroid and look "healthy" (Hetzel & Pandav, 1996). Children born in iodine deficient areas are at risk of mental retardation due to combined effects of maternal, fetal and neonatal hypothyroidism (Glinoer & Delange, 2000). Bleichrodt & Born (1994) showed 13.5 IQ points deficit due to iodine deficiency. In Indonesia, Muhilal (1998) estimated 130 million points IQ lost due to iodine deficiency.

Ngargoyoso sub-district, being a mountainous area on the high slope of Mount Lawu, is an IDD endemic area. The prevalence of goiter among schoolchildren increased steadily from 29% in 1996 (Kauldhar, 1996) to 32% in 2006 (DoH, 2006) and 51.9% in 2010 (Suprapto et al, 2010). In 2004 the government of Indonesia officially banned the use of iodine capsules for IDD eradication and replaced it with iodized salt. However, universal salt iodization is still facing many problems (Djokomoeljanto, 2004). Last survey (2011) in Ngargoyoso sub-district revealed that only 61% household used iodized salt (Reistanti, 2011). It is much below the government target (>90%) (MoH, 2000). People in Ngargoyoso sub-district drink water from spring wells through pipelines directly to their homes, unfortunately it contains no iodine and contaminated by E.coli (Dewi, 2010). Although the water is free, it must be added with iodine and boiled to be safe drinking water. Kendi (water-pitcher) is an earthenware ceramics made from clay. It has been used in Java (Adhyatman, 1987) and Southeast Asia (Rooney, 2003) for many centuries for rituals and traditional drinking water. Drinking water must be boiled before pouring into the kendi. So that it is hygienic.

Kendi is very cheap and its volume can be controlled easily.

While universal salt iodization is far from being achieved in Ngargoyoso sub-district and the community has water resources for free from the nature it is very logic to add iodine into the drinking water as a supplement to the salt iodization program.

Iodine supplementation trial on school children improved cognitive function (van den Briel et al, 2000; Zimmermann et al, 2006; Gordon et al, 2009). However, there is no such trial on preschool children conducted (Melse-Boonstra & Jaiswal, 2010). Preschool children living in iodine deficient area are vulnerable (Hartono, 2001) Therefore, an iodine supplementation trial to preschool children is warranted. The objective of the study was to test hypothesis that iodine supplementation into drinking water presented in kendi increased urinary iodine excretion and intelligence quotient among preschool children aged 25-59 months in Ngargoyoso sub-district, Central Java, Indonesia.

2. Subjects and Methods

2.1 Research Setting

The study took place in the rural area of Ngargoyoso sub-district on the high slope of Mount Lawu, Central Java, Indonesia, at an altitude of about 900 meters above the sea level. It has some asphalt roads, traditional markets, electricity, 58 integrated health posts and a health center. The most remote area has no access for four-wheels car. It consists of 9 villages with inhabitant around 30.000 people living from subsistent farming; only four villages with the highest goiter prevalence included in the study. People drink water from spring wells through pipelines directly to their homes. The water contains no iodine. Iodized salt is widely distributed in the markets with higher price than un-iodized one. Less than 90 % households used iodized salt for cooking. Since the year 2004 iodized oil has been withdrawn from Indonesia IDD elimination program, including in the study area. Total goiter rate (TGR) in Ngargoyoso sub-district increased steeply from 29% in 1996, to 32% in 2006, and 51.9% in 2010 after stopping the supply of iodized capsules.

2.2 Subjects

Three hundreds and seventeen preschool children aged 25-59 months initially agreed to participate in the study. They were screened for their urinary iodine excretion (UIE). Seventy four children with UIE less than 100µg/L (23.3%) were asked to enter the study by using the following inclusion criteria:

1. Age 25-59 months at baseline.
2. Urinary iodine excretion < 100µg/L.
3. Not breastfed anymore.
4. Agreed to participate in the whole study.

Children with cretinism, mental retardation, severe malnutrition, congenital malformations, or their siblings suffered from goiter were excluded from the study.

Only sixty seven preschool children finished Stanford-Binet intelligence test successfully. They were then allocated randomly using random table into two groups: treatment (TG) and control group (CG). Treatment group received 100µg/day of iodine, and CG received placebo (distillated water) for twelve weeks. Potassium-iodate was used as supplements, because it does not change the color, taste and odor. Both the children and the researchers did not know the member of the groups. The Head of the Health Center kept the list and opened it at the end of the study, just before the analysis.

2.3 Study protocol

List of preschool children aged 25-59 months living at four villages in Ngargoyoso sub-district was used as baseline data. Midwives in charge then invited the mothers to visit the health center for briefing. Mothers who agreed to participate in the study filled and signed an informed consent. They were asked to collect their children's urine using a plastic bottle (± 50 ml, with a cap and without preservative). The midwives collected urine from the mothers at integrated health posts. On the next day, all samples without refrigeration were sent to IDD Laboratory at Magelang, Central Java, for urinary iodine excretion measurement.

Sixty seven preschool children aged 25-59 months were tested for intelligence score using Stanford–Binet Scale. The results were recorded as baseline data. After randomization, TG and CG received 100µg iodine/day and placebo for twelve weeks, respectively. Data on UIE, IQ scores, nutritional status, nutrient intakes, social economic and care practices were taken before and after supplementation for comparison.

To ensure compliance, midwives visited the mothers at their home and change the empty bottles of supplements with the new ones. The study was undertaken between July and November 2011.

2.4 Urinary iodine measurement

Urinary iodine excretion (UIE) was measured by using Method A, (WHO, 2007) ammonium persulfate digestion (Sandell-Kolthoff reaction). Casual urine samples were taken without preservative and refrigeration in plastic bottles in the morning, and then sent to IDD laboratory at Magelang, Central Java on the next day. Results were reported in µg/L urine.

2.5 Intelligence testing

Psychological test was conducted at the health center by a team from the Department of Psychology, Faculty of Medicine, Sebelas Maret University, at baseline and 12 weeks after treatment. Stanford-Binet Scale was used for assessing children's intelligence, because it has been adapted in Indonesia by the Department of Psychology, Gadjah Mada University. Intelligence score was expressed as IQ point.

2.6 Dietary assessment

An estimated record technique with a 24 hour recall was used to assess dietary intake of the subjects. One of the researchers undertook the interview and analyzed the nutrient intake using Nutrisurvey for Windows™ Software Package (Erhardt, 2005) for energy, protein, and iron.

2.7 Anthropometric measurements

Weight was recorded on a calibrated mechanical bathroom scale to the nearest 0.1 kg (Krups, Ireland) after zeroing for each measurement. Children were lightly clothed and had removed their footwear. Height was recorded using a microtoise (Statumeter™, Indonesia) and measured to the nearest 0.1 cm. Each child stood with his buttocks, heels and back against the wall and his head in the Frankfurt plane. Data was analyzed using WHO-Anthro software package (adapted for Indonesia, 2005) and the results were reported as z-scores for weight/age, height/age and weight/height.

2.8 Supplements

To provide 100µg iodine/L drinking water, the following procedure was used: 24 g of KIO3 diluted with adding 725 ml distillated water. This solution is then poured into 24 plastic bottles of 30 ml each. Two drops of this solution is added to 10 L of drinking water. This provides 200µg iodine per liter of drinking water (Pandav et al, 2000). Thus, to obtain 100µg iodine per liter of drinking water, we put one drop of the solution to 10 liters of drinking water. The supplement does not change the color, taste and odor of the drinking water. Drinking water from pipelines was boiled before supplemented. This drinking water was presented to the children in a "kendi" (water-pitcher). The volume of the "kendi" is about one liter each. "Kendi" is an earthenware ceramics made from clay. It has been used in Java (Adhyatman, 1987) and Southeast Asia (Rooney, 2003) for many centuries for ritual and traditional drinking water containers. It is hygienic and cool.

2.9 Statistical analysis

Results were expressed as the mean ± standard deviation. To see the difference between baseline and post-treatment in each group a paired *t*-test was used. For comparison between groups an independent *t*-test was used. Chi-square was used when appropriate. All statistical analysis was performed using SPSS for Windows, release 17.0 (Chicago, IL, USA).

2.10 Ethical considerations

The study was approved by the Ethical Review Committee, School of Medicine, Sebelas Maret University. The mothers on behalf of their children were informed about the nature of the study and agreed to participate in the study.

3. Results

Three hundreds and seventeen preschool children aged 25-59 months were screened for their UIE. There were 74 (23.3%) children with UIE < 100µg/L. Seven children were excluded from the study because of not attending or not finishing the psychological testing at baseline. Sixty seven preschool children aged 25-59 months with UIE < 100µg/L were randomly allocated into TG (n=33) and CG (n=34). Table 1 showed the characteristics of the subject at baseline.

Twelve weeks post-treatment all data were recollected and compared with baseline data. (Table 2). There was no dropout, both mothers and children enjoyed the drinking water presented in"kendi", because it is convenience and cool. Urinary iodine excretion increased from 62.45 ± 26.21 µg/L to 244.55 ± 120.19 µg/L in the treatment group. The IQ scores also increased from 101.48 ± 11.03 to 110.27 ± 9.04 points in the treatment group.

4. Discussion

Indonesia is the biggest archipelago in the world. Java is one of the most populated islands with more than 80 million inhabitants. It has some pockets of IDD in mountainous area. Ngargoyoso sub-district is one, -among others- , which is classified as severely endemic according to WHO (2007) classification. It is located on the high slope of Mount Lawu at an altitude of ± 900 m. It has two Hindu's temple, Cetho and Sukuh, come from the late of Madjapahit's kingdom (1293-1500). In the past, "kendi", a traditional drinking water, was used in rituals and daily living (Adhyatman, 1987; Rooney, 2003). People put "kendi" filled with boiled water in front of their home for street-walkers in case they are thirsty they can drink it. "Kendi" reflects togetherness. The government of Indonesia is trying to preserve the custom.

"Kendi" was chosen to keep drinking water in this study for some reasons. First, it is hygienic, as the water must be boiled before pouring into the "kendi". Second, as "kendi" is hand made from clay, it is still porous for oxygen get through inside the water and makes it cool and fresh. Third, it is easy to control the volume of drinking water. One liter "kendi was used in this study. Fourth, to support the government of Indonesia in revitalizing the use of "kendi" in the community.

Since the year 2004 the government of Indonesia withdrew iodine capsules from its IDD elimination program, so that children and pregnant women in Ngargoyoso sub-district relied their iodine intake on iodized salt. Unfortunately, some problems with iodized salt still exist, namely: price, coverage, distribution, and low iodine concentration (Djokomoeljanto et al, 2004). People in Ngargoyoso sub-district get drinking water from spring-wells which contain no iodine and contaminated by E.coli. Boiling drinking water, pouring it into a "kendi" and then dropping iodine manually is logically fixing the problems. The study revealed that acceptance of "kendi" was very good, the mothers and the children liked it and no dropout found.

The study, as far as our knowledge, was the first iodine supplementation trial conducted on preschool children aged 25-59 months in relation to intelligence. There were some studies on preschool children < 5 year old using multiple micronutrients supplements with conflicting results (Eilander, 2010). Preschool children living in iodine deficient area are vulnerable (Hartono, 2001) for two reasons. First, iodine concentration in breast-milk of mothers living at developing countries is low. (Allen, 1994). Second, breast-milk concentration declines over the first six months post-partum in iodine-deficient women (Mulrine et al, 2010). Preschool children aged 25-59 months in the study area receive no more breast-milk from their mothers. Although brain development slowdowns after two years old (Uauy et al. 2001) cell differentiation, myelination, and synapses formation still continued. The human brain achieves its full size at eleven years old (Nolte, 2009), even Black and Ackerman (2008) suggests that cognitive function can be improved until fifteen years old. Several studies conducted on school children recently proved the efficacy of iodine supplementation on improving cognitive performance (van den Briel, 2000; Zimmermann et al, 2006; Gordon et al, 2009). Benton & Cook (1991) found that iodine supplementation on six year old children for six weeks can improve intelligence score by 7.6 points. In the present study, iodine supplementation of 100μg/d into drinking water presented in "kendi" for twelve weeks increased UIE and IQ points, 182 μg and 8.8 points, respectively. Margin of safety for iodine supplementation is very large, however, iodine excess has not shown significant role in children's intelligence (Qian et al, 2002).

Intelligence is influenced by many factors. Some other nutrient deficiencies such as iron (McCann & Ames, 2007) has significant deleterious effect on cognitive function. Therefore, we compared nutrient intakes of CG and TG (Table 1 and Table 2) before and after supplementation and found no significant difference between groups. McGregor (1995) reviewed the effect of severe malnutrition on cognitive development. She found significant deleterious effect of severe malnutrition on cognitive function. In this study, we also compared nutritional status of the two groups and found no difference between CG and TG. Socioeconomic factors, caring practices and maternal education associated with cognitive development of the children (Wachs et al, 2005). Eilander et al (2010) showed that micronutrient supplementation also influenced by age, nutritional status, nutrient intakes and socioeconomic factors. In our study, all these factors were equal between groups.

Drop method has been successfully used in Thailand for school children (Pandav et al, 2000) in reducing goiter rates. It costs $0.001/d. In our study, the cost for 100μg/d of iodine supplementation was less than $0.001/d (based on the current rates). It is very cost-effective and affordable. The people at the study area get their drinking water from spring wells for free of charge from the nature.

The present study had many strengths. First, it was the first iodine supplementation trial conducted in preschool children aged 25-59 months. Second, it was a randomized, double blind, placebo controlled trial. Third, the compliance over the study period was excellent, no dropouts and no side effects reported. Kendi was acceptable, cost effective, and affordable. Fourth, all confounding factors to intelligence were elaborated and compared to ensure that iodine supplementation of drinking water by drop method, presented in "kendi" was the sole cause of the increment of IQ scores by 8.8 points. Fifth, based on the results of the study a prompt action was taken by the Head of the Health Center at Ngargoyoso sub-district to provide 100 mg iodized capsules (Yodiol™, Kimia Farma, Indonesia) to all preschool children living in the study area. The only limitation of the study was its relatively short duration of 12 weeks. Therefore, a larger and longer study is needed to ascertain whether the changes seen in this study are replicable, and a follow up study to ensure that the changes are permanent.

5. Conclusion

Iodine supplementation into drinking water presented in kendi is an effective way to increase intelligence quotient among preschool children aged 25-59 months in the study area.

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Figure 1 Flow diagram of the trial

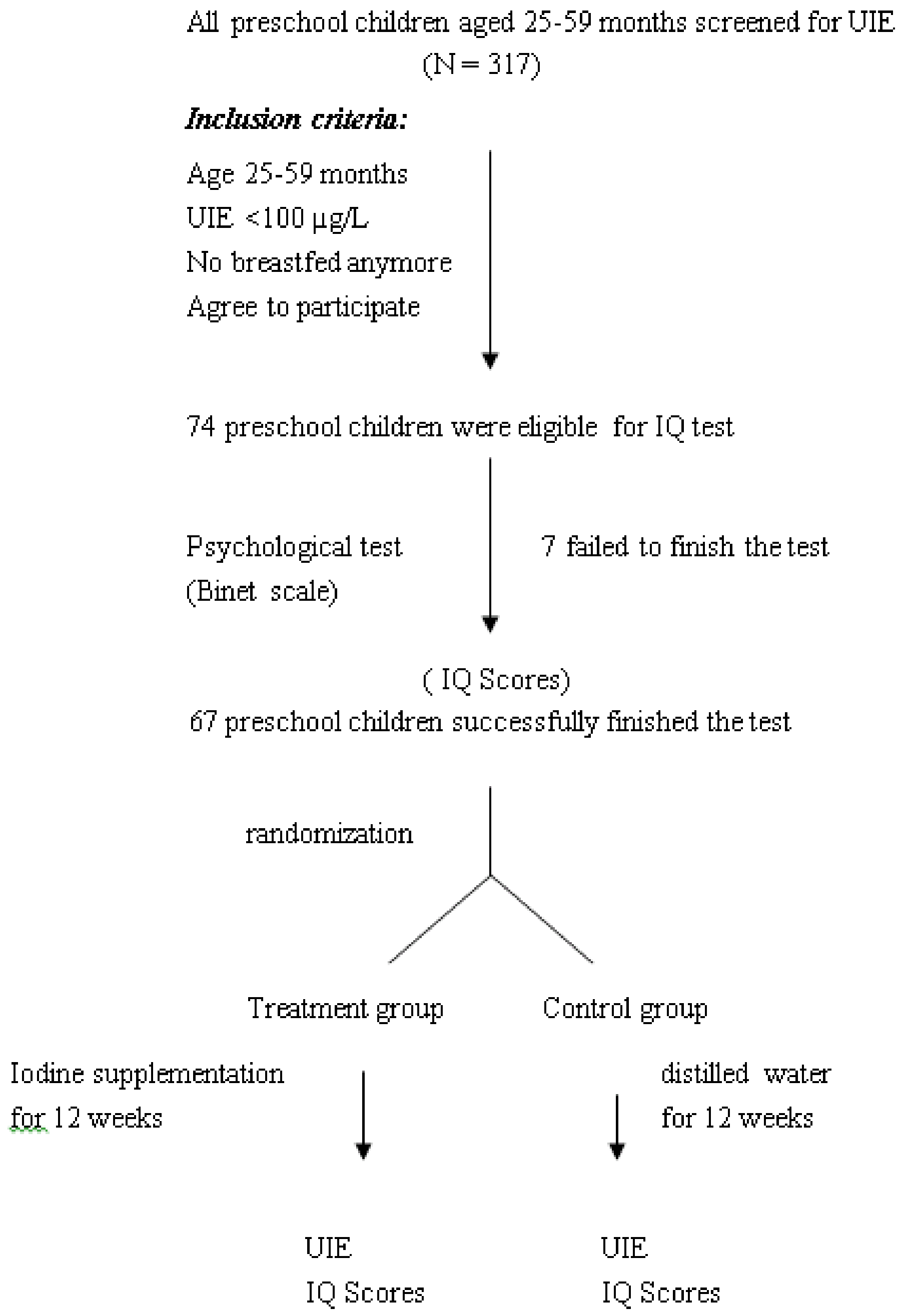

Table 1. Characteristics of the subjects at baseline.

Variable	Control group (CG)			Treatment group (TG)				
	n	Mean	SD	n	Mean	SD	t	p
Age (month)	34	35.85	7.98	33	40.12	10.05	1.93	0.058
Sex								
Male	21					25	$X^2 = 1.52$	0.218
Female	13					8		
Nutritional status:								
z-score W/A	34	-0.96	1.03	33	-0.70	0.82	1.11	0.272
z-score H/A	34	-1.67	1.99	33	-1.54	1.74	0.28	0.778
z-score W/H	34	0.01	1.62	33	0.30	1.72	0.72	0.471
Energy intake (kcal/day)	34	721.07	166.36	33	703.60	379.52	0.25	0.807
Protein intake (g/day)	34	28.40	10.19	33	29.60	18.02	0.34	0.737
Iron intake (mg/day)	34	6.65	8.51	33	6.89	8.37	0.12	0.905
UIE (µg/L)	34	71.15	22.32	33	62.45	26.21	1.46	0.148
IQ (points)	34	105.18	9.62	33	101.48	11.03	1.46	0.149

Table 2. Comparison of baseline data with twelve weeks after supplementation between control group and treatment group.

Variable	Control group (CG)			Treatment group (TG)				
	n	Mean	SD	n	Mean	SD	t	p
UIE baseline (µg/L)	34	71.15	22.32	33	62.45	26.21	1.46	0.148
UIE 1 mo (µg/L)	34	125.53	44.77	33	223.61	93.83	5.49	<0.001
UIE 3 mo (µg/L)	34	120.00	79.77	33	244.55	120.19	5.01	<0.001
IQ baseline (points)	34	105.18	9.62	33	101.48	11.03	1.46	0.149
IQ 3 mo (points)	34	103.06	9.99	33	110.27	9.04	3.04	0.003
Z-score W/A (baseline)	34	-0.96	1.03	33	-0.70	0.82	1.11	0.272
Z-scroe H/A (baseline)	34	-1.67	1.99	33	-1.54	1.74	0.28	0.778
Z-score W/H (baseline)	34	0.01	1.62	33	0.30	1.72	0.72	0.471
Z-score W/A (3 mo)	34	-0.99	1.10	33	-0.84	0.90	0.59	0.557
Z-score H/A (3 mo)	34	-1.79	1.18	33	-1.90	1.45	0.35	0.726
Z-score W/H (3 mo)	34	0.07	1.14	33	0.41	0.97	1.32	0.191
Energy(Kcal/d)baseline	34	721.07	166.36	33	703.60	379.52	0.25	0.807
Energy (Kcal/d) 3 mo	34	850.73	245.73	33	805.25	452.55	0.51	0.610
Protein (g/d) baseline	34	28.40	10.19	33	29.60	18.02	0.34	0.737
Protein (g/d) 3 mo	34	32.03	10.92	33	34.11	22.51	0.48	0.631
Iron (mg/d) baseline	34	6.65	8.51	33	6.89	8.37	0.12	0.905
Iron (mg/d) 3 mo	34	5.75	6.81	33	5.76	8.40	0.01	0.995