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Stabilizing 30ppm Iodine in Iodized Salt: The Effect on Iodine Status and Thyroid Function in Children

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ABSTRACT

Background: Salt iodization considers an effective way of ensuring iodine sufficiency, but a wide variation range of household salt iodine levels existed. Research in iodized salt intervention on preschool-age children had not been found.
Objective: Analyse the effect of stabilizing 30 ppm household iodized salt for six months on iodine nutrition status and thyroid function.
Method: This was a pre post-test experiment study, with 76 preschool-age children in a replete iodine area in Purworejo Regency. Iodized salt at 30ppm was given for six months. Thyroid function (TSH and FT4) were assessed at 0 and 6 months. Iodine status (UIE) were assessed at 0, 3, and 6 months. ANOVA RM mixed methods were used to interpret the result.
Results: Before the study, 51.9% of households had an inadequate level of iodized salt. There were a significant increase of TSH ($t=-3.184$; $p<0.000$). FT4 significantly decreased, ($t=6.686$; $p<0.001$) but all still in the normal range. Means of UIE also increase significantly (25.95; $p=0.000$) towards excess (225μg/L vs 349μg/L). The main effect of iodine intake baseline status showed UIE increased differently between groups ($F = 12.82$; $p = 0.000$). Iodine status among groups of subjects initially excess decrease after three and six months. On the contrary, subjects initially deficient at baseline, after six months showed the highest mean of UIE.
Conclusion: Iodine status significantly increased. Preschool-age children who initially deficienct become groups with the highest iodine intake level. Monitoring iodine intake in population groups and policy on adjusting prophylaxis iodized salt is important.

Keywords: Iodized salt, preschool-age, iodine status, thyroid function

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INTRODUCTION

Iodine is a crucial micronutrient prerequisite for optimal growth and development, through its vital role in thyroid hormone synthesis (Ellsworth *et al*., 2020), (Nerhus *et al*., 2019). Iodine is a main element of thyroid hormones. Therefore, hypothyroidism and hyperthyroidism are among non-communicable diseases highly related to nutrition. Deficiency or excess of iodine intake related to increased occurrence of thyroid disorders (Laurberg *et al*., 2010), (Møllehave *et al*., 2018), (Leung & Braverman, 2017), (Weng *et al*., 2017). Salt iodization is considered an effective way to ensure iodine sufficiency and optimizing thyroid function. But they're still a problem with a wide variation range of iodine levels in household salt. Researches on the iodine sufficiency in salt among small salt producers in India, household salt surveys in 11 countries, and household salt surveys in Morocco and Tunisia showed similar problems. The experience of salt surveillance in Morocco only shows that iodized salt only use in one out of four households. The concentration of iodine in salt was expected between 15-40 mg/kg and only fulfilled in 4.5% of the sample, 8% of households use coarse salt and mostly happened in rural areas. Research in 11 small and medium-sized countries showed households using iodized salt coverage increased from 46.3% to 52.4%, from 2000 to 2010. Tunisia, with national UIE, showed adequate level still had problems with the disparity of household iodized salt quality, with only 50% use sufficient iodized salt (15-25 ppm). Children in deprived households had more risk of iodine deficiency status and less access to adequate iodized salt. After the two decades of the Universal Salt Iodization (USI) program, the 90% coverage was still out of reach and requires more effort efforts (Doggui *et al*., 2017), (Tran *et al*., 2016), (Zahidi *et al*., 2016). Basic National Research Data in 2013 as the latest national research that included iodized salt assessment, showed 77% USI coverage in Indonesia. Problems with disparities between regions and the wide variation of iodine levels in household salt still exist (Fuada, 2018).

Experience in various countries shows that various age groups respond to prophylaxis iodized salt in different ways. Research in Zhejiang (China), Konya (Turkey), and Nigeria showed, while the iodized salt program can meet children iodine intake, the needs of pregnant women as vulnerable groups still show slight deficiency (Hess *et al*., 2017), (Zhifang Wang *et al*., 2018), (Isiklar Ozberk *et al*., 2019). On the other hand, some research also showed a tendency toward iodine intake excess after the prolonged iodized salt program and could impair (Doggui *et al*., 2017), (Palaniappan *et al*., 2017). Most evaluation on salt iodization program reporting school-age children or childbearing age, pregnant, and breastfeeding women (Dold *et al*., 2018), (Hess *et al*., 2017), (Hutchings *et al*., 2018), and mostly without ensuring the stability of iodine level in salt. Evaluation studies on iodized salt programs revealed, ensuring the sufficiency of iodine status in pregnant and breastfeeding women could heighten the risk for excess in children (Sun *et al*., 2017). Pre-school age is an important life cycle due to their still rapid growth and development. But research on iodine status and thyroid function of pre-school age children is still scarce (Nerhus *et al*., 2019), and no previous studies found on the impact of salt iodization intervention on preschool-age children. This research will analyze the effect of stabilizing 30 ppm household iodized salt for six months on preschool-age children iodine nutrition status and thyroid function. Baseline iodine nutrition status and households iodine level in salt were also considered in the intervention impact.

MATERIALS AND METHODS

This paper is part of a study on the effect of giving 30 ppm iodized salt and cognitive stimulation on preschool-age children living in the IDD area. Previous articles reported the impact of three months of cognitive stimulation and iodized salt intervention on iodine status and cognitive development in preschool-age children living in replete iodine deficiency areas. The result showed no difference found on iodine status, and no assessment conducted on thyroid (Latifah *et al*., 2013). The intervention extended until six months, and thyroid function was assessed. All subjects were given 30ppm household iodized salt for six months. This paper focused on the effect of stabilizing household iodized salt for six months on preschool-age children's iodine status and thyroid function concerning the prior household iodized salt level and baseline iodine status. The study has approval from The National Institute of Health Research and Development Ethics Committee (KE.01.09./EC/598), Indonesia. Research information is given verbally and in written to the mothers before signed informed consent on behalf of their preschool-age children.

It was a one-group pre and post-test experiment study, with 76 preschool-age children in a replete iodine area in Purworejo Regency. Field permit for research process were obtained from Integrated Licensing Service Office Purworejo Regency (072/268). The interventions given were 30ppm iodized salt for six months. Iodine level of 30 ppm were chose, following the Indonesian National Standard (INS) recommendation of minimum level of iodized in salt (Samsudin *et al*., 2016). The iodized Iodized salt intervention specially manufactured to contain 30 ppm of KIO3. The iodine manufactured were under Ir. Marihati supervision, a researcher with long-term experience in salt industry researches. She was working in a research and development center under the Ministry of Industry, Indonesia. Based on WHO data, the average consumption of iodized salt is 10 grams/person/day. In this study, the number of household members in each family assumed to be five people. That way, each family needs 10 grams x 5 people = 50 grams salt/day. Researchers distributed iodized salt every two months. Assuming one month is 30 days, the salt given to each family each time is 50 grams x 2 months x 30 days = 3000 grams = 3 kilograms. Salt was distributed in the form of brick salt. Families returned the unexpended salt to the researcher, and then three kg of new salt is given for the next two months.

When giving iodized salt to the respondent, information was given on several matters so that the interventions carried out were on target: (a) Information on the use of iodized salt. It is important to mention that the iodized salt given is only used for daily family consumption. Using salt for animal food, or for cooking food not used for family members was prohibited. Families also were not allowed to use salt from other sources for cooking family food. (b) Information on using iodized salt in the cooking process. It is advisable to put salt at the end of the cooking process to preserve the iodine in the salt. (c) Information on how to store iodized salt. The researcher also provided the information in the form of leaflets.

UIE as iodine nutritional status indicator were assessed at 0, 3, and 6 months intervention. Household iodized salt level before intervention assessed with titration. EIU status was measured as the amount of iodine excreted in the urine. UIE was an indicator of iodine intake. Health analysts collected a sample of 25 cc or ½ bottle spot urine for analysis. Health analysts have also taken a blood sample. Blood is drawn as much as three cc in the area of the venous media cubiti by using a Terumo needle of 3 ml. Spectrophotometer method with the BIO brand tool RAD SmartSpecTM Plus model built in California, the USA in 2003 used to analyzed the UIE levels. TSH and FT4 levels were indicators of thyroid function. ELISA method using BIO-TEK brand Elx 800 model made in Vermont, the USA in 1995, utilized to analyzed TSH and FT4 level at 0 and 6 months intervention. Researchers interpret the result using paired sample t-tests and ANOVA mixed methods-repeated measures.

RESULTS

This research found a wide variation of iodine levels in household salt before the intervention. The range differs from inadequate to the high iodine level in household salt (Table. 1). A significant percentage of low iodine levels in salt found among subjects (51.3%). The mean of iodized salt was above the intervention level (40.24ppm). Risk of excess (UIE >300μg/L) found among 30.3% and 17.1% deficient (UIE <100μg/L).

Table 1. Baseline Household Salt and Thyroid Function by Baseline Iodine Status

	mean	n	%
Household salt Iodine level (ppm)			
<30ppm		39	51.3
30-40ppm		8	10.5
>40ppm		29	38.2
TSH	2.55		
fT4	1.72		

After six months of intervention on preschool children in repleted iodine deficiency area, iodine level at six months increases significantly (Table. 2). While the baseline iodine intake showed a more than adequate iodine intake level (225.0 μg/L), after six months of intervention, the iodine intake showed excess (349.0 μg/L). On the contrary, fT4 decreased (although all subjects still in the normal range), TSH increased significantly, demonstrated a tendency toward subclinical hypothyroidism. Cases of hypothyroidism slightly increase from 2% to 7.9% at the end of the intervention.

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Tabel 2. Mean different test on iodine status and thyroid function at 0,3, and 6 month

	0 month n(%)	3rd month n(%)	6th month	t/F	P
TSH (µIU/ml) x̄ (SD)	2.55(1.43)		3.18(0.12)	-3.184§	0.000
TSH status < 0.3 µIU/ml 0.3-6.2 µIU/ml > 6.2 µIU/ml	 1(1.3) 73(96.1) 2(2)		 1(1.3) 69(90.8) 6(7.9)	5.096#	0.278
fT4 (µIU/ml) x̄ (SD)	1.48 ± 0.12		1.30± 0.25	6.686§	0.001
fT4 status <0.3 µIU/ml 0.8-2.0 µIU/ml > 2.0 µIU/ml	 0 (0.0) 76 (100) 0 (0.0)		 0 (0.0) 76 (100) 0 (0.0)	-	-
UIE(µg/L) median (SD)	225.0±193	234.0±130	349.0±158	25.95¶	0.000
UIE status <100 µg/L 100-199 µg/L 200-299 µg/L >300 µg/L	 13 (17.1) 21 (27.6) 19 (25.0) 23 (30.3)	 7 (9.2) 22 (28.9) 22 (28.9) 22 (32.9)	 4 (5.3) 6 (7.9) 19 (25.0) 47 (61.8)		

§paired sample t-test; ¶ANOVA Repeated Measure #chi square

Tabel 3. Summary of iodine intake difference at 0,3, and 6 month based on baseline iodine status and household iodized salt

Variable and source	Df	SS	MS	F	P
Time	2	932927.94	469034.68	25.95	0.000
Baseline iodine status x time	4	961605.05	242361.11	13.38	0.000
Baseline iodized salt x time	4	7036.53	3518.27	0.196	0.822
Error	142	2552240.88	17973.53		
Baseline iodine status	2	555614.38	266249.64	12.82	0.000
Baseline iodized salt	1	48613.96	135990.92	4.471	0.127
Error	71	1446741.91	20376.65		

Further analysis using mixed method ANOVA repeated measure showed the main effect of initial household iodine salt levels is not significant (Table. 3). The UIE aggregate change did not differ between groups of subjects whose iodine levels in household salt were initially adequate and inadequate (F = 0.196; p = 0.822). The main effect of baseline UIE significantly different (F = 13.38; p = 0.000). UIE increased in the group of subjects who were initially deficient was significantly higher than in other groups. Mean of iodine status among groups of subjects initially excess decrease after three months and also six months. On the contrary, subjects initially deficient at baseline, after six months of intervention, showed the highest mean of UIE compare to other groups (figure 1).

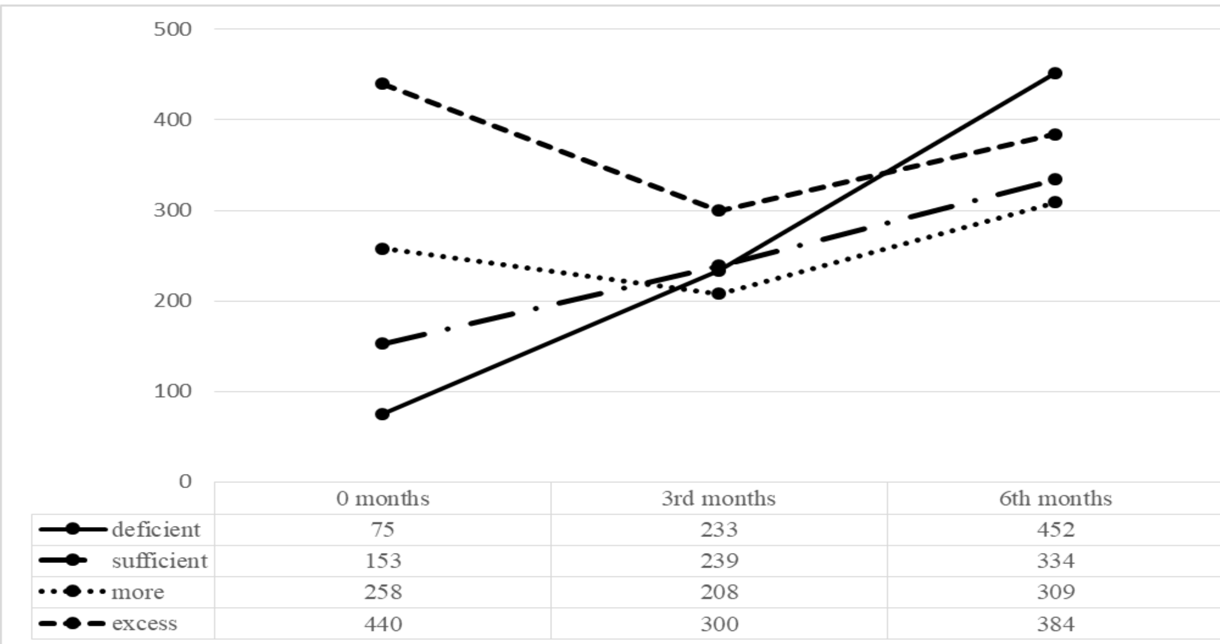

Figure 1. Median UIE at 0,3, and 6 month based on baseline iodine status

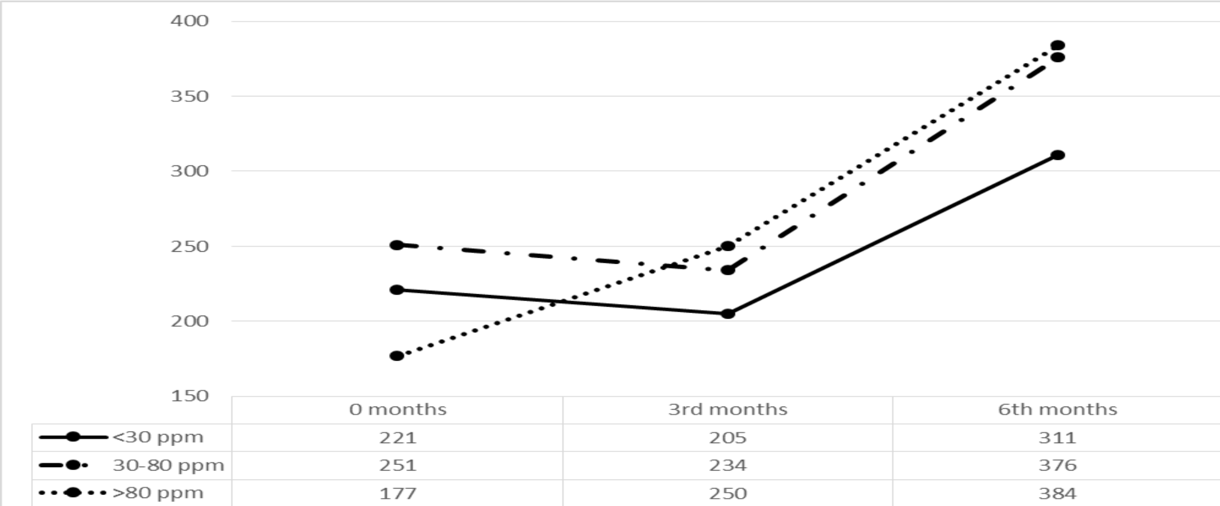

Figure 2. Median of UIE iodine intake at 0,3, and 6 month based on baseline household iodized salt

DISCUSSION

As reported earlier, three months of stabilizing 30 ppm iodized salt intervention did not change preschool-age children's iodine intake status in replete iodine deficiency areas. Thyroid status has not been evaluated in three months of intervention (Latifah *et al*., 2013). Extending the intervention time to six months turned out to have a significant impact on iodine status, and also thyroid function. This research was taken in an area previously found as an endemic IDD as concluded from median UIE on childbearing age women in Pituruh based on baseline research conducted one year before (Kumorowulan *et al*., 2013). Since then, the district government also intensely intervened in Pituruh with the IDD elimination program before this research was conducted. It could explain the high level of iodine status and normal range of FT4 and TSH at baseline. Like other countries' experience, this research found a similar problem of a high variety in salt iodine level. Even the median UIE showed adequate or more than adequate intake, there still a significant proportion in population unprotected from IDD due to different access to iodized salt (Doggui *et al*., 2017), (Tran *et al*., 2016), (Zahidi *et al*., 2016), (Knowles *et al*., 2017). Researches on IDD usually were conducted on school children and childbearing age women. It is interesting to examine how younger age children respond to iodized salt intervention in controlled salt iodine levels.

After six months of the intervention of giving 30ppm iodized salt, there was a significant increase in iodine status from more than adequate to excess (225 µg/L to 346 µg/L) accompany by alteration in fT4 and TSH level among preschool-age children. Before and after the intervention, fT4 still in the normal range, but several subclinical hypothyroidism was existed due to heightened TSH levels. Previous research found excessive iodine intake can alter thyroid function. Different from this research, several studies found hyperthyroidism due to excess iodine (Thomopoulos, 2002), (Roti & Degli Uberti, 2001), (Lind *et al*., 1998). Increased hyperthyroidism in former iodine deficiency towards iodine sufficiency area. A high iodine intake leads to the increased prevalence of overt hypothyroidism also observed in Austria after four years of salt iodination (Lind *et al*., 1998). Prophylaxis of salt iodization leads to decreasing TH and heightened T4 and T3 also found in Bangladesh, in an area that previously had iodine adequate level (Parveen *et al*., 2009). Several studies worldwide observed similar patterns. The excessive intake of iodine leads to an increased prevalence of subclinical hypothyroidism. In Korea, it is due to iodine seaweed rather than iodized salt (Kang *et al*., 2018). The hypothyroidism prevalence is higher in areas with excess iodine after the iodized salt program in China (Shan *et al*., 2016). Compared to a 1999 study, the prevalence of subclinical hypothyroidism, positive TPO Ab, and TgAb also increased. Despite the successfully attained goals of iodine elimination in China, there is a record of iodine intake's negative contribution to the prevalence and variation of thyroid problems (Kang *et al*., 2018).

There are several explanations for the increase in subclinical hypothyroid problems in excess conditions. Researches showed the prevalence of subclinical hypothyroidism was significantly higher in the iodine deficiency, and iodine excessive groups compared to those in the adequacy group (UIC 100-299.9 µg/L). Therefore, correlation between serum levels of TSH and free T4 with UIC were formed in a U-shape and inverted U-shape (Laurberg *et al*., 2010), (Zheng *et al*., 2018). Epidemiological studies revealed that hypothyroidism is more prevalent in populations with a high iodine intake. The higher prevalence of subclinical hypothyroidism after a higher intake of iodine is attributable to increasing serum TSH levels. The impact was previously shown in an animal model. High iodine levels were proven to inhibit iodothyronine deiodinase activity in the hypothalamus and/or pituitary. A decreased conversion of T4 to T3 was revealed. A disruption of the negative feedback regulation responded by increasing TSH secretion. Probably, this is also a complication to thyroid adaptation to iodine intake. Many thyroid processes were inhibited when iodine intake becomes high, and the frequency of apoptosis of follicular cells becomes higher (Laurberg *et al*., 2010); (Li *et al*., 2012).

This research also found that children with an initial status of iodine deficient showed a significantly higher increase in iodine nutrition status towards excess. The way the human body compensating for the usually low iodine supply involving complex mechanisms developed in the thyroid gland. Mechanisms can even store and utilize iodine in very small provisions. The thyroid immediately responds to an abrupt load of iodine to avoid the thyroid hormone overproduction. Typically, complex mechanisms could hightened the prevalence of dysfunction and non-communicable diseases. A slightly increased prevalence of higher serum TSH may be observed already when iodine intake is brought from mildly deficient to adequate (Laurberg *et al*., 2010), therefore it could be more prevalent with a wider difference.

This contrary to our expectations. Stabilizing 30 ppm household iodized salt for six months expected to optimize iodine intake and thyroid function in preschool-age children. Before the intervention, the percentage of preschool-age children with an indication of excess had exceeded deficiency (17.1% vs 30.3%), with the condition that 51.3% of households consumed salt <30ppm. After the intervention of stabilizing 30ppm iodized salt, the prevalence of deficiency decreased (5.3%) and excess doubled (61.8%). Experience in Shanghai and Sweden shows the importance of evaluating iodine interventions from time to time. Government implements regular UIE surveillances concerning the adequacy of household iodized salt. The results contribute to policy changes related to salt iodization. Shanghai enacted several decreases in iodine salt levels in response to a higher prevalence of excess iodine intake, while Switzerland increased iodine level in household iodized salt in response to iodine intake deficiency (Z Wang *et al*., 2019).

Several limitations and also strengths present in this research. The subjects were limited without a control group, but it was replaced by assessing the effect of initial household salt consumption and iodine deficiency conditions. Iodine source not only came from iodized salt, but also from food. A research conducted in several region in central Java identified food rich in iodine content, such as milk, egg, beef, freshwater fish. The iodine from plants varies, and related to iodine level in water and soil (Kusumawardani *et al*., 2017). The iodine intake from food was also haven't considered in this research. This research presents a clear finding of the higher risk of excess iodine status after the intervention of iodized salt in preschool-age children with deficient iodine intake.

CONCLUSIONS

After 30ppm iodized salt intervention for six months, iodine intake significantly increased in preschool-age children living in a replete iodine deficiency area. The iodine status of preschool children who previously had deficiency iodine nutrition status increased in the direction of excess. Thyroid function showed significant alteration, fT4 levels decreased, TSH levels were increased, followed by increased cases of subclinical hypothyroidism.

Increased risk of thyroid disorders could be associated with lower and upper limit of iodine nutritional status from the recommended interval. Therefore, we should keep iodine intake in a population within an adequate interval. Iodine deficiency disorders are prevented, but also does the excess. Monitoring iodine intake in different groups of the population is important, and it is related to adjusting policy on prophylaxis iodized salt level. Further research could try other iodized salt levels. Iodine intake from other sources than salt and different confounding factors related to iodine status and thyroid function also needed to be considered.

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