Cognitive and Motor Functions of Iodine-Deficient but Euthyroid Children In Bangladesh Do not Benefit from Iodized Poppy Seed Oil (Lipiodol)[1]

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ABSTRACT Iodine supplementation before pregnancy in iodine-deficient women prevents cretinism and neuromotor deficits in their offspring. It is unclear whether iodine supplementation benefits cognitive function in iodine-deficient school-aged children. We therefore conducted a double-blind, randomized, controlled trial of the effects of iodized poppy seed oil (Lipiodol) on cognitive and motor function and weight gain of iodine-deficient school children. The study was conducted with 305 children in grades 1 and 2 from 10 primary schools in two iodine-deficient areas in Bangladesh. The children were stratified by school and grade and randomly assigned to receive 400 mg of oral Lipiodol or a placebo. All children were given a battery of cognitive and motor function tests and had their weights, serum thyroxine (T_4) and thyroid-stimulating hormone (TSH) and urinary iodine levels measured before and 4 mo after the intervention. On enrollment, both groups were moderately iodine deficient (median urinary iodine values: placebo group = 3.3 μmol/L, n = 148; iodine group = 3.1 μmol/L, n = 152; goiter prevalence in both groups >95%). However, their T_4 and TSH levels were within the normal range. After 4 mo, there was a significant treatment effect on urinary iodine levels ($P < 0.0001$), but the levels of the treated group were still below normal (median = 7.9 μmol/L). No significant differences were found in T_4 and TSH levels, weight gain, cognitive or motor function. The findings suggest that Lipiodol supplementation in moderately iodine-deficient children with normal T_4 levels is unlikely to benefit their cognitive function. However, it remains possible that other iodine preparations may have benefits. J. Nutr. 131: 72–77, 2001.

KEY WORDS: • *iodine deficiency disorders* • *iodized poppy seed oil* • *cognitive functions* • *school children* • *urinary iodine excretion*

An estimated 2.2 billion people are at risk of iodine deficiency (1). Severe iodine deficiency in utero causes developmental defects in animals (2) and cretinism and increased neonatal mortality in humans (3). A number of trials of iodine supplementation of mothers before or during pregnancy (e.g., 4–6) have also shown that children of supplemented mothers performed better at motor and cognitive tests than children of unsupplemented mothers or mothers supplemented later in pregnancy. There is also some evidence that the developmental levels of infants supplemented in y 1 of life may benefit, but not the incidence of neurologic abnormality (4). However, little is known about the effects of iodine deficiency occurring in later childhood on children's cognitive function. Many observational studies have shown an association between iodine deficiency and poor cognition in school children (7). But it is not possible from observational studies to separate the effects of poor environment and previous intrauterine exposure to iodine deficiency from those of current iodine deficiency. To determine whether iodine deficiency in later childhood causes poor cognition, a randomized controlled trial of iodine supplementation is necessary.

Several supplementation trials in children have been conducted (8–13), but only two were randomized, controlled trials (8,13). In both of those studies, the children were supplemented with iodized poppy seed oil, Lipiodol. In the Bolivian study (8), children with low urinary iodine levels showed no benefit to their intelligence quotients from supplementation. However, there was a significant increase of the urinary iodine levels in the placebo group, suggesting that they also had an increased iodine intake. In the other randomized trial in Malawi (13), children with severe urinary iodine deficiency were studied. The group treated with Lipiodol showed a significant improvement in one of three motor function tests 11 mo after the intervention. A large difference was shown in all cognitive function tests between the placebo and treated group at the time of follow-up. Unfortunately, the baseline cognitive function data were considered unreliable and thus were not used; both groups were severely deficient in urinary iodine measures at the post-treatment test. Thyroxine (T_4)[3] levels were not reported in either of the latter two studies.

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[3] Abbreviations used: IDD, iodine deficiency disorders; T_4, thyroxine; TSH, thyroid-stimulating hormone.

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We previously reported (14) that school children in iodine-deficient areas in Bangladesh who had had low T_4 levels had poorer cognitive function and school achievement levels than children with higher T_4 levels. This finding remained after controlling for a comprehensive number of socioeconomic and biological factors. We report here the results of a randomized, controlled trial of Lipiodol on cognitive and motor function and weight gain of children living in the same area.

SUBJECTS AND METHODS

Study site

Two severely iodine-deficient rural areas in Bangladesh, Gopalpur and Shibpur (median urinary excretion < 1.58 μmol/L and goiter prevalence $> 60\%$), were selected from a recent national Iodine Deficiency Disorders (IDD) survey by the Institute of Nutrition and Food Science, Dhaka University (15). The areas are located in the flood-prone and plain zones of the country. The population consists mainly of small farmers or agricultural laborers.

Subjects

One year before the study began, all children in 10 primary schools in grades 1 and 2 (mean age 9.8 $\pm$ 1.3 y, mean $\pm$ SD), who were present when the schools were visited, were requested to give a finger prick blood sample. The blood was stored on filter paper; serum T_4 and thyroid-stimulating hormone (TSH) levels were later assessed at the Institute of Child Health, London, UK.

One year later, we returned to the area and all children who had previously had T_4 levels <51 nmol/L (below the lowest reference range in the supplied kit) and remained in the schools, were enrolled into the study ($n = 305$). They were stratified by school and grade and randomly assigned to receive 400 mg of oral Lipiodol or a placebo that had similar appearance and taste and contained the poppy seed oil without iodine.

Procedure

Before the treatment, all children were given a battery of cognitive and motor function tests, their weights and heights were measured, and samples were taken of venous blood and casual urine for estimation of serum T_4, TSH and urinary iodine levels. Four months after treatment, all of these measures were repeated except for height. All of the children's homes were visited once and a detailed socioeconomic history was taken from their parents.

The Bangladesh Medical Research Council's ethical review committee and the ethical review committee of Great Ormond Street Hospital for Sick Children, Institute of Child Health, London, UK, approved the study protocol. Both parents and children gave verbal consent.

Measurements

The measurements have been described in detail previously (14); therefore only a brief discussion will be given here.

Anthropometry. Heights and weights were measured using standard techniques (16). Two persons did the anthropometric measurements and interobserver reliability was high ($n = 30$; height, $r = 0.99$; and weight, $r = 0.99$).

Serum T_4 and TSH. At enrollment, a 5-mL venous blood sample was collected from the children. At the 4 mo follow-up, blood spots were collected from each child on Guthrie cards. Serum T_4 and TSH levels were analyzed in both the blood spots and venous blood samples. The samples were assayed by coat-a-count neonatal T_4 assay technique, which is a solid phase ^{125}I RIA. TSH samples were assayed by the Gamma-BCT-Neo-TSH technique, which is a two-site immunoradiometric assay. Diagnostic Products, Los Angeles, CA supplied the kits for both assays. The findings from the enrollment (venous sample) and 4-mo (blood spot) analyses were compared in the placebo group and they were not significantly different.

Urinary iodine. Iodine levels in casual urine samples were measured at the Institute of Nutrition and Food Science, Dhaka University by an adapted wet digestion method (17).

Socioeconomic status. Parents were interviewed at home and information was sought concerning the families' sociocultural and economic conditions. Six interviewers gave the questionnaire and interobserver agreement was high. Complete agreement was achieved with the trainer in a minimum of 90% of the questions, in 10 consecutive interviews for each interviewer, before the study began.

For analyses, the responses to each question were rated with poor being low and good higher. The items were then grouped into four indices based on theoretical considerations and the ratings in each index were summed. The indices included *stimulation materials index* (presence of children's books, adult books and toys); *possession index* (possession of radio, TV, cassette player, beds, tables and chairs); *house index* (condition of roof and wall, source of drinking water, presence of electricity, type of latrine and number of people per room); and *animal index* (possession of chickens, pigeons, ducks, goats and cows). The educational level, occupation, reading, and writing ability of the parents were also determined.

Cognitive and motor function tests. A range of cognitive functions was assessed. Functions thought to be affected by biological insults including hypothyroidism (13,18–20), neonatal hypothyroidism (21), short-term food deprivation (22) and parasitic infections (23) were assessed. The children did not have to be able to read to do any of the tests. Extensive pilot tested of the tests occurred before the study began and adaptations were made where necessary for Bangladeshi children.

The following cognitive function tests were used:

Verbal fluency. This test measures the speed of semantic processing and is considered to be an indicator of the central executive component of working memory (24). The child has to repeat as many words as possible in 1 min in two categories, animals and things to eat.

Digit span. The test measures working memory (24). The child has to repeat strings of numbers of increasing length.

Visual search. This test measures the speed of visual information processing and sustained attention (25,26). The child has to search rows of different pictures on a page and mark target pictures as quickly as possible with a pencil.

French learning test. This test is a measure of paired associate learning (24). It consists of pictures whose names are to be learned in an unfamiliar language (French) in a set number of trials.

Corsi blocks. This is a measure of visuospatial working memory (27). The child is presented with an array of black blocks and has to touch a series of them in a specific order. The series is increased in length until the child makes errors.

Ravens Colored Progressive Matrices. This measures visual reasoning ability (28).

Symbol symbol modalities test. This test measures paired associate learning and speed of information processing and was modified from the Symbol Digit Modalities Test (29) used in an adult hypothyroid study (20). The children are first presented with two shapes, which are each paired with a picture. The children are then shown two pages of the same shapes arranged in random order in rows and asked to name the pictures paired with them as fast as possible.

Modified Stroop. This test measures the speed of information processing and ability to inhibit responses. The child is shown two pages of six rows of black and white circles arranged randomly and asked to touch each circle and name the opposite color, i.e., when touching black to call out white. The average speed of correctly naming a circle is the score.

Upper limb speed and dexterity. The child has to make dots with a pencil in 3 rows of small circles as quickly as possible. This was modified from a subtest of the Bruinincks-Oseretsky Test of Motor Proficiency (30). The time taken to dot all circles is the score.

The Lafayette peg board (Lafayette Instrument, Lafayette, IN). This is a measure of fine motor coordination. The pegs looked like keys and have to be rotated to match the holes before they can be inserted. The time taken to place the pegs with both the dominant and nondominant hand is measured.

Six graduates in psychology or education, who were unaware of

the children's group assignment, administered the tests to the children. After training, before the study, each tester tested 20 children twice, 7 d apart; test retest reliability was more than $r = 0.7$ for each cognitive test for each tester.

Ten percent of all tests given throughout the study were observed by a second tester and scored independently. The testers rotated among themselves and the intertester correlations were all higher than $r = 0.98$.

Data analyses

The distribution of each variable was examined for normality, and appropriate transformations were made where necessary. Four cognitive and motor tests (visual search, Stroop, peg board dominant and nondominant), serum TSH and urinary iodine levels were log transformed. Differences between the treatment groups at enrollment in cognitive and motor test scores and other normally distributed variables were examined using ANOVA, controlling for age and sex where relevant. The χ^2 test with continuity correction and the Mann-Whitney U test were used to examine differences in nonnormally distributed variables. Heights were expressed as Z-scores of the National Center for Health Statistics reference data (31) and body mass index was calculated from weight (kg)/height^2 (m^2).

The treatment effects of iodine on the children's cognitive and motor tests, weights, T_4, TSH and urinary iodine levels were examined with stepwise multiple regression analyses. In these analyses, each outcome variable, measured at the postintervention assessment, was used as the dependent variable in separate multiple regressions. In the first step, the relevant initial measure, age and sex were entered as independent variables followed by treatment group (iodine = 1, placebo = 0) in a second step.

RESULTS

Loss from the study

At 4 mo, 11 children (7%) in the iodine group and 7 children (5%) in the placebo group were not at school on the days when testing occurred. There was no significant difference between the lost children and those tested in any of their characteristics on enrollment shown in **Table 1** or their scores on the cognitive tests.

Children's characteristics

One hundred fifty-six (156) children were given iodine and 149 children received placebo treatment. The children's nutritional status was generally poor; the mean height-for-age and weight-for-age were less than −2 Z-scores. There was a high prevalence of goiter according to the WHO classification (32). Only 5.1% of the iodine group and 4% of the placebo group had no palpable or visible goiter (grade 0). Grade 1 goiter (palpable but not visible when neck is in normal position) occurred in 51.3 and 49.7% of the iodine and placebo groups, respectively and grade 2 goiter (visible when neck is in normal position) occurred in 43.6 and 46.3% respectively. A population with a prevalence of 5–19.9% goiter is classified as having mild iodine deficiency, one with 20–29.9% as moderate and >30% as severe deficiency (32). The population would therefore be classified as severely iodine deficient by goiter prevalence. Around 50% of the families were very poor, subsisting on casual laboring; 60% of fathers and 72% of mothers had no schooling. There were no significant differences between the groups in any of the socioeconomic or nutritional variables, age or sex distribution. There was also no significant difference between the groups in the stimulation materials, animals, possessions and housing indices.

Biochemical thyroid functional measures

On enrollment, mean serum T_4 and TSH values were not significantly different between the iodine and placebo group and were within the normal ranges of reference values (33) (Table 1). Iodine deficiency is classified by the median value for urinary iodine levels as follows (μmol/L): severe = < 1.58; moderate = 1.58–3.87; mild = 3.95–7.82; and no deficiency = >7.9 (32). In this study, both groups would be classified as moderately iodine deficient by urinary iodine excretion (median value 3.1 and 3.3 μmol/L, respectively, for iodine and placebo groups). Most (85%) of the children had excretion levels below normal (7.9 μmol/L).

Treatment effects were examined in a series of stepwise multiple regressions of the final measurements of urinary iodine, T_4 and TSH in turn. The independent variables were the

TABLE 1

Thyroid hormones, urinary iodine levels and body weight of the children in iodine and placebo groups at enrollment and after 4 mo, and regression coefficients (B) for treatment effect from multiple regression analyses[1]

Thyroid function measures and weight	*n*	Iodine group	*n*	Placebo group	Treatment effect		
					B	SEM	*P*-value
T_4,[2] *nmol/L*							
Enrollment	138	97.1 ± 24.6	139	98.2 ± 24.2			
4 months	122	106.1 ± 34.2	126	101.6 ± 31.2	5.4	4.0	0.18
TSH,[3] *mU/L*							
Enrollment	138	1.44 ± 2.3	139	1.46 ± 2.1			
4 mo	122	1.62 ± 1.80	126	1.72 ± 1.69	−0.03	0.03	0.31
Urinary iodine,[3] *μmol/L*							
Enrollment	142	2.76 ± 2.19	141	2.86 ± 2.28			
4 mo	138	6.83 ± 1.94	139	3.31 ± 3.06	0.31	0.06	<0.0001
Weight,[2] *kg*							
Enrollment	156	21.0 ± 3.2	149	21.2 ± 3.3			
4 mo	145	22.1 ± 3.1	142	22.2 ± 3.3	0.08	0.15	0.59

[1] Model for multiple regression analyses: dependent variable was the relevant outcome measurement at the 4-mo test and independent variables were initial measurement, age, sex and treatment group.
[2] Arithmetic means ± SD.
[3] Geometric mean ± SD.

relevant initial values, age, sex and treatment group. A significant treatment effect ($P < 0.0001$) was observed only for urinary iodine excretion, where the iodine-treated group increased more than the placebo group. The treatment effect was not significant for serum T_4 or TSH.

Weights

Mean body weights of the children increased significantly in both groups. This increase in weight was independent of age and treatment, but girls increased significantly ($P < 0.01$) more in weight than boys. A multiple regression analysis predicting final weight and controlling for age, sex and initial weight showed no significant treatment effect (Table 1).

Cognitive functions

Cognitive and motor function tests scores on enrollment and after 4 mo are shown by treatment group in **Table 2** in those children who completed the study. There was a consistent improvement in cognitive and motor test scores in both groups. However, there were no significant differences between the treatment and placebo groups in any of the cognitive or motor function measures after 4 mo.

Multiple regression analyses of the final scores of each cognitive and motor test indicated that treatment was not significant in any test after taking into account sex and age. Controlling for social background variables did not change the results. The regression coefficients and standard errors for the treatment effect are shown in Table 2.

DISCUSSION

We conducted a double-blind, randomized, controlled treatment trial of oral Lipiodol in children who were moderately iodine deficient according to their urinary iodine excretion, severely deficient according to goiter prevalence but biochemically euthyroid. We found no benefit to the children's cognitive and motor functions or weight gain over 4 mo. Both groups improved over the 4 mo in cognitive or motor test scores. This is a normal finding and is attributed to both practice and maturation.

The randomization in the treatment trial was satisfactory, showing no significant differences in baseline levels of T_4,

TABLE 2

Cognitive and motor test scores in iodine and placebo groups at enrollment and after 4 mo and regression coefficients (B) and standard errors for treatment effect from multiple regression analyses[1]

Cognitive and motor tests	Iodine group (n = 145)	Placebo group (n = 142)	Treatment effect		
			B	SEM	*P*-value
Corsi block					
Enrollment	10.66 ± 1.95	10.60 ± 1.86	0.20	0.19	0.42
4 mo	11.36 ± 1.71	11.20 ± 1.81			
Digit span					
Enrollment	5.47 ± 1.29	5.68 ± 1.30	0.10	0.14	0.46
4 mo	5.92 ± 1.29	5.95 ± 1.40			
French learning					
Enrollment	30.23 ± 6.16	30.68 ± 6.54	−0.04	0.70	0.71
4 mo	31.89 ± 6.41	32.41 ± 7.23			
Ravens Matrices					
Enrollment	13.10 ± 3.27	12.72 ± 2.74	0.15	0.36	0.69
4 mo	14.88 ± 3.28	14.60 ± 3.19			
Verbal fluency					
Enrollment	24.87 ± 5.97	25.06 ± 5.49	0.01	0.56	0.73
4 mo	28.51 ± 5.45	28.45 ± 5.50			
Visual search[2,3]					
Enrollment	2.72 ± 1.25	2.72 ± 1.25	−0.001	0.01	0.47
4 mo	2.18 ± 1.24	2.21 ± 1.20			
SSMT[2]					
Enrollment	0.89 ± 0.19	0.89 ± 0.21	0.02	0.01	0.19
4 mo	0.79 ± 0.17	0.78 ± 0.15			
Stroop[2,3]					
Enrollment	1.04 ± 1.3	1.03 ± 1.3	0.01	0.01	0.42
4 mo	0.92 ± 1.3	0.90 ± 1.2			
Peg board dominant[2,3]					
Enrollment	91.26 ± 1.2	89.23 ± 1.2	−0.01	0.01	0.15
4 mo	77.57 ± 1.2	78.13 ± 1.2			
Pegboard non-dominant[2,3]					
Enrollment	109.04 ± 1.2	107.92 ± 1.2	0.002	0.01	0.56
4 mo	95.28 ± 1.2	93.82 ± 1.2			
ULSD[2]					
Enrollment	26.47 ± 5.33	26.04 ± 4.86	0.11	0.36	0.89
4 mo	24.64 ± 4.12	24.38 ± 3.83			

[1] Model for multiple regression analyses: dependent variable was the relevant outcome measurement at the 4-mo test and independent variables were initial measurement, age, sex and treatment group. SSMT, symbol modalities test. ULSD, upper limb speed and dexterity.
[2] Time in seconds, lower score is better.
[3] Geometric mean ± SD. All others are arithmetic mean ± SD.

TSH, urinary iodine, cognitive or motor function test scores between the iodine-treated and placebo groups. There was also no difference in socioeconomic and biological variables between the placebo and iodine-treated groups. In addition, the groups were matched for school and grade.

The sample size was calculated on the assumption of detecting a difference of 0.5 SD between the groups in cognitive and motor function test scores at a power of 80–90%; thus the study had adequate power. In addition, the testing was controlled rigorously, a wide range of functions was assessed and 4 mo should have been long enough for benefits to appear.

The children's serum T_4 and TSH values were within the normal range initially, and no significant treatment effect on T_4 or TSH was found. It appears that the children's thyroid function had adapted to the low iodine intake. Normal T_4 and TSH values are often found in the presence of urinary iodine deficiency (e.g., 34). A significant treatment effect was found on urinary iodine levels with a clear increase in the treated group. Although the urinary iodine levels in the treated group at 4 mo were more than double initial levels, they were not within the range of normal values. Recent studies have shown that rapeseed oil (35), peanut oil (36) and Oriodol (37) may produce greater and longer lasting increases in iodine levels.

We had originally planned to study only children with low T_4 levels; however, in the year between screening and commencing the study, the children's T_4 levels improved substantially, although there was no formal iodization program in the area. We are unsure how some iodine had come into the area; however, at the time of enrollment, the children remained moderately iodine deficient as measured by urinary iodine excretion. Furthermore, the urinary iodine levels of the placebo group remained stable throughout the study period, indicating no further increase in iodine status.

This population of children would have been classified as iodine deficient by the usual public health methods, and may well have been targeted for iodized oil supplementation. Therefore the question we posed was the following: does this level of iodine deficiency affect children's cognition? The findings suggest that low urinary iodine and high goiter prevalence in the presence of normal thyroid function does not affect cognition.

There are several possible interpretations of these findings. One hypothesis is that cognitive deficits occur in iodine-deficient children only in the presence of hypothyroidism. If this is correct, assessing thyroid hormones would give a better indication of the risk of cognitive deficits than urinary iodine or goiter prevalence. It may be that most of the cognitive deficits often found in euthyroid children in iodine-deficient areas are due to previous exposure to intrauterine iodine deficiency and are irremediable at this age. Another hypothesis is that the iodine preparation (Lipoidol) was not sufficiently effective, and it is possible that other preparations that produce normal levels of iodine excretion may have had benefits.

Because policy decisions concerning iodine supplementation are often made on the basis of population measures of urinary iodine excretion and goiter prevalence, these results remain relevant. We found no published, randomized, controlled trial of iodine supplementation in school children that showed clear benefits to their cognitive function.

In conclusion, our study showed that iodine deficiency as measured by urinary iodine was accompanied by goiter, but not by hypothyroidism. Presumably there was effective trapping of iodine for thyroid hormone synthesis by hyperactive thyroid glands. It is therefore perhaps not surprising that iodine supplementation failed to enhance cognition in euthyroid children. It may be that the cognition of other children who have lower T4 levels would be amenable to iodine supplementation. It will be possible to determine this only if future studies include children with low T4 levels as well as low urinary iodine.

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