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Thyroid Hormone Supplementation in Preterm Infants Born Before 28 Weeks Gestational Age and Neurodevelopmental Outcome at Age 36 Months

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Background: Thyroid hormones are required for normal brain maturation, and neonatal plasma thyroid hormone concentrations are low in infants less than 28 weeks gestation. It is not known whether treatment of such infants with thyroid hormone improves neurodevelopmental outcome.
Methods: At three years corrected age, mental, motor, and neurological development was assessed in infants born at less than 28 weeks gestational age who had participated in a phase 1 trial of differing doses and modes of administration of thyroid hormone. The trial's endpoints were thyroid hormone (thyroxine, T4) and thyotropin plasma concentrations in eight study arms: six treated with T4 [4, 8, and 16 μg/(kg·day)], bolus or continuous], one treated with iodine only, and one treated with placebo. Follow-up at three years was not part of the original study goals. Developmental index scores, rates of cerebral palsy (CP), and rates of adverse outcome (death or moderate to severe delay in development and/or disabling CP) were compared between the eight study groups and between groups combined by dosage level, and between infants with and without T4 supplementation.
Results: Of 166 randomized infants, 32 (19%) died in the neonatal period. Of the 134 survivors, follow-up results were available for 89 children (66%). Mental and motor development and rates of cerebral palsy did not differ in any of the comparisons made.
Conclusion: In this study, no differences in neurodevelopment were found in relation to thyroid hormone treatment, but power was insufficient to detect any but very large differences.

Introduction

Thyroid hormones are essential for brain development throughout gestation and the first years after birth (1). Thyroid hormones and their receptors are present in the human brain prior to the onset of fetal thyroid function (2). During the first half of pregnancy, maternal thyroid hormone supplies the fetus with thyroid hormones. Maternofetal thyroid hormone transport is regulated by trophoblast cell membrane transporters, which mediate influx and efflux of thyroid hormones. In addition, placental deiodinases and transthyretin, which provide transport roles in the placenta, are involved (3). As gestation progresses, the fetal thyroid gland is increasingly able to produce thyroid hormones, but transplacental maternal thyroxine (T4) still contributes to the fetal thyroid hormone pool (4).

T4 is the major secreted product of the thyroid gland. After transport through the blood–brain barrier, it is deiodinated to the bioactive triiodothyronine (T3) in astrocytes, and T3 is subsequently actively transported into the adjacent neuron, where it primarily acts as a gene regulator via binding to the nuclear thyroid hormone receptors. Binding of the receptor T3 complex to a thyroid hormone responsive element in the promoter region of a gene will subsequently lead to increased (or decreased) transcription of target genes (5). There are also nongenomic actions of T4, especially involved in actin polymerization in neurons, which is important in migration and projection formation (5). For these pathways involved in brain maturation, the T4 plasma supply, but not necessarily the T3 plasma supply, needs to be sufficient.

After extremely premature birth (i.e., before the 28th week of gestation), the maternal contribution is abruptly interrupted

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at a time when the hypothalamo-pituitary-thyroid axis and thyroid hormone regulation is still immature. After extremely premature birth, plasma concentrations of T4, T3, free T4 (FT4), and free T3 and thyroxine-binding globulin (TBG) are lower than in infants of higher gestational ages, and thyrotropin (TSH) elevation is not seen. This period of low thyroid hormone levels is referred to as transient hypothyroxinemia of prematurity (THOP) (6).

Low T4 and FT4 concentrations in the neonatal period are associated with worse neurodevelopmental outcome at two to five years of age for premature infants (10–13). Despite this relationship, the question as to whether T4 supplementation leads to improvement of child development or to a reduction in neurodevelopmental impairments is still unresolved (9,14).

We conducted a multicenter phase 1 clinical trial of four thyroid hormone replacement regimens of varying dosage and type of delivery (bolus or continuous infusion) in infants of less than 28 weeks gestational age (15). The goal of the trial was to compare thyroid hormone concentrations in the plasma across the four thyroid hormone treatment arms, and the iodine only and placebo arms. The aim was to determine which treatment regimen elevated (F)T4 concentrations into the euthyroid range with least suppression of TSH. Two additional thyroid hormone supplementation study groups (bolus and continuous) were inadvertently added due to a dosing error (which led to doubling of the maximum T4 dosage of 8 μg/d; i.e., to 16 μg/d) in one of the three patient enrollment sites. Neurodevelopmental follow-up of the participating surviving infants was not preplanned, but was organized after completion of the initial study. Here we present neurodevelopmental follow-up results at the corrected age of three years in relation to the eight study groups.

Methods

Study population and exclusions

As reported before (15), the study was approved by the Institutional Review Boards of the three clinical enrollment centers (in Westchester County, NY; Amsterdam, the Netherlands; and Madrid, Spain) for neonates born between 24 0/7 and 27 6/7 weeks gestation and enrolled in the first 24 hours after birth. Excluded were mothers less than 18 years old or with thyroid disease or reported substance abuse (i.e., alcoholism or use of heroin or methadone, as these substances can interfere with hormone transport in serum) and newborns with major congenital malformations or if death was expected within 48 hours.

Study design and intervention

Thyroid hormone (Bedford Labs Pharmaceuticals, Amerisource Bergen) was administered from postnatal day 1 to postnatal day 42 in four treatment arms as T4 at 4 or 8 μg/(kg·d) delivered either as a bolus intravenous (i.v.) injection (1 mL/kg in 5% dextrose) or via continuous i.v. infusion [0.5 mL/(kg·d)]. When converting to oral dosing via gavage, bolus administration was kept as once a day regimen, while continuous administration was changed to a four times per day dosing regimen, with T4 dosing increase by 25% to accommodate intestinal losses. In each study arm, 20–28 infants were entered. Due to a dosing error in the Madrid pharmacy, 15 infants received 16 μg/(kg·d) as a bolus ($n=7$) or as continuous infusion ($n=8$). T3 was provided to all four T4 treated arms at 1.0 μg/(kg·d) in a continuous intravenous infusion for the first 14 postnatal days as immediately available active hormone. Subjects in the continuous infusion arms who were fully enterally fed had the appropriate amount of study drug added to ingested milk every 4 to 6 hours. To better understand whether negative iodine balance plays a role in neonatal thyroid hormone levels, one arm of the study was provided with iodine (Upsher-Smith, 30 μg/(kg·d) in 1 mL aqueous oral solution. The placebo arm received 5% dextrose [0.5 mL/(kg·d), i.v. or PO].

Randomization was done by a web-based computer program, which balanced gestational age, sex, and center.

Clinical definitions and management strategies

Gestational age was based on the best estimate of the attending neonatologist at birth, using obstetrical parameters and examination. Necrotizing enterocolitis was recorded if greater than Bell's stage II (at least proven by abdominal X-ray), retinopathy was recorded of prematurity as greater than stage III in either eye, and chronic lung disease was recorded as oxygen requirement at 36 weeks to keep oximeter saturations greater than 88–90%, as described in the original report (15). Cranial ultrasounds were made throughout the hospital stay, and germinal matrix hemorrhages and periventricular leukomalacia were scored according to the extremely low gestational age neonates (ELGAN) study protocol (16).

Iodine precautions

The United Stated and the Netherlands are considered iodine replete countries, while in Spain this is not always the case. Maternal FT4 levels did not differ between sites. The study protocol called for avoidance of iodinated skin cleansers for antisepsis as excess exposure to iodine suppresses thyroid hormone synthesis. Instead, chlorhexidine (2% w/v 70% v/v ethanol) was used for skin disinfection with careful removal using sterile water after 30 seconds to avoid chemical burns of the skin.

Data monitoring

Clinical status was recorded daily for two weeks and once per week thereafter in a web-based spreadsheet until hospital discharge. Cranial ultrasound imaging was conducted on postnatal days 1–3, 7–10 and after at least 4 weeks and was interpreted by a single radiologist (Paula Brill, MD), masked to the study arm. FT4 was measured using the equilibrium dialysis technique and the other hormones by standard immunoassay technology (Quest Diagnostics).

Neurodevelopmental follow-up

At the corrected age of three years, surviving children and their parents were invited to the follow-up clinics in each of the three institutions. Development was assessed using the *Bayley Scales of Infant and Toddler Development*, third edition (BSITD III) (17). Trained psychologists masked to the study arm administered the cognitive and motor scales. The manual of the Bayley scales was used as guideline for assessment in all three sites, and no formal intercenter training session was carried out. The original U.S. norms were used in all three centers. The cognitive scale assesses

abilities such as sensorimotor development, exploration and manipulation, object relatedness, concept formation, memory, and simple problem solving, while the motor scale consists of fine motor (grasping, perceptual-motor integration, motor planning, and speed) and gross motor (sitting, standing, locomotion, and balance) subtests. The cognitive outcome is reported as the composite cognitive scale, which has a mean of 100 and a standard deviation of 15. Scaled scores are used for the Fine and Gross Motor scores separately, which have a mean of 10 and range from 1 to 19. Children were also assessed by blinded pediatricians for cerebral palsy (CP). The criteria for the diagnosis of CP included abnormal tone, motor control, and function. The severity of CP was scored using the Gross Motor Function Classification System (GMFCS) (18).

Because follow-up was only planned after conclusion of the initial pharmacology trial, it was sometimes difficult to convince parents to come to the clinic without any specified incentives, particularly in the United States. In case of an overdue assessment, we performed an alternative, more age-appropriate test of cognitive development. Scores on such tests were only used in the overall calculations of abnormal outcome. Moderate to severe delay in cognitive development was defined as a developmental age of more than six months below the corrected age at testing. As an index of socioeconomic status, the number of years of maternal education after elementary school was recorded in the children who underwent follow-up.

Statistical analyses

For analyses of differences between the study arms, we used both parametric and nonparametric tests. Thus, analysis of variance and the Kruskal-Wallace test were used for continuous variables, and for dichotomous variables, the chi-squared test or Fisher exact test (when expected cell size was less than five) were used. We report findings for the parametric tests. In a second analysis, outcome results were analyzed for combined arms (placebo plus iodine, compared with the combination of the 4, 8, and 16 μg T4 bolus and continuous arms). In a third analysis, the placebo plus iodine arms in combination were compared with results from all T4 supplementation arms combined. First we examined cognitive and motor scores and the numbers of CP cases per treatment arm. Then we made a combined measure of adverse outcome defined as postnatal death or CP with GMFCS of two or higher (disabling CP) and/or moderate to severe cognitive delay using the BSITD III or any alternative cognitive test (a score on these tests of greater than one SD below the mean). For statistical analyses, SPSS software version 18 was used.

Results

In this study, 166 of the 168 children described in our first publication formed the study cohort available for examination where the parents of one infant withdrew consent before initiation of the study and another study participant was diagnosed with a 22 Q11 deletion syndrome (14). Of these, 32 (19%) infants died in the neonatal period, leaving 134 available for outpatient follow-up. The parents of 45 children could either not be traced or refused follow-up. Follow-up results were thus available for 89 of the children eligible for follow-up (66%).

Table 1 illustrates the perinatal characteristics of infants in whom follow-up results were and were not available. Apart from differences in follow-up across centers, there were no significant differences between those two groups. Nevertheless, the group in which no follow-up was accomplished tended to be somewhat sicker, with a longer mean duration on ventilatory support and had a longer total hospital stay consistent with a higher degree of illness. Table 2 compares the same perinatal demographic characteristics among the eight original pharmacological study arms; again, no differences were found across treatment arms.

Table 3 compares neurodevelopmental outcomes. In the total group of 89 children, CP occurred in 9% of subjects where 5% had a GMFCS level 1. The mean cognitive composite score was 99.2. Scaled fine and gross motor score in all infants averaged 11.1 and 9.3 respectively. There were no significant differences either between the eight arms or between the arms combined per dosage (no hormone supplementation versus 4 versus 8 versus 16 μg T4). There were also no differences between children who did or did not receive any T4. Since in the Netherlands follow-up was 98%, we also analyzed whether analyses with Dutch children only would change the results, which was not the case. The

Table 1. Perinatal Characteristics of Surviving Children With and Without Follow-Up at the Corrected Age Three Years

	No follow-up n = *45*	*Follow-up* n = *89*
Center		
New York *n* (%)	36 (80)	25 (28)*
Amsterdam *n* (%)	1 (2)	41 (46)
Madrid *n* (%)	8 (18)	23 (26)
Maternal schooling after elementary school, years, mean ± SD	6.7 ± 3.5 *n* = 6	7.0 ± 3.2 *n* = 87
Gestational age, weeks	26.0 ± 1.1	26.3 ± 1.0
Birth weight, grams	832 ± 181	887 ± 193
Male, *n* (%)	21 (47)	51 (57)
Pulmonary status on ventilator, days mean ± SD	24 ± 46	15 ± 19
Oxygen requirement at post-menstrual age, days *n* (%)	19 (42)	33 (37)
ROP > 3, *n* (%)	4 (9)	8 (9)
IVH 3 or 4, *n* (%)	6 (13)	7 (8)
PVL, n (%)	4 (9)	9 (10)
Treated with indomethacin, *n* (%)	22 (49)	39 (44)
Surgical ligation of patent duct, *n* (%)	8 (18)	14 (16)
NEC, *n* (%)	6 (13)	7 (8)
Surgery for NEC, *n* (%)	1 (2)	2 (2)
Episodes with antibiotics, *n* (%)		
No antibiotics	11 (24)	16 (18)
1 or 2 episodes	24 (53)	58 (65)
> 2 episodes	8 (18)	13 (15)
Duration of hospital stay, days mean ± SD	99.5 ± 55.2	89.1 ± 28.2

*$p < 0.01$. No other significant differences between the two arms.
IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity; SD, standard deviation.

Table 2. Perinatal Characteristics of Children in Whom Follow-Up Was Done, by Study Arm

	Placebo n = *13*	*Iodine* n = *14*	*Bolus 4 μg/kg* n = *10*	*Continuous 4 μg/kg* n = *18*	*Bolus 8 μg/kg* n = *11*	*Continuous 8 μg/kg* n = *15*	*Bolus 16 μg/kg* n = *3*	*Continuous 16 μg/kg* n = *5*	*Total* n = *89*
Maternal schooling after elementary school, years, mean ± SD	8.8 ± 2.5 *n* = 13	7.5 ± 2.5 *n* = 14	7.9 ± 2.2 *n* = 10	7.7 ± 2.1 *n* = 18	5.2 ± 3.4 *n* = 10	6.1 ± 4.4 *n* = 14	4.7 ± 4.2 *n* = 3	4.8 ± 4.6 *n* = 5	7.0 ± 3.2 *n* = 87
Gestational age, weeks	26.5 ± 1.3	26.2 ± 1.2	26.1 ± 0.8	26.5 ± 0.9	26.1 ± 0.9	26.2 ± 1.1	26.7 ± 0.6	26.5 ± 1.0	26.3 ± 1.0
Birth weight, grams	910 ± 202	909 ± 196	876 ± 214	888 ± 254	863 ± 122	876 ± 161	867 ± 170	875 ± 222	887 ± 19
Male, *n* (%)	9 (70)	7 (50)	6 (60)	7 (39)	8 (73)	11 (73)	1 (33)	2 (40)	51 (57)
Ventilator days, mean ± SD	13 ± 20	19 ± 27	7 ± 12	8 ± 8	16 ± 13	20 ± 24	37 ± 18	16 ± 14	15 ± 19
Oxygen requirement at 36 weeks pma, *n* (%)	5 (38)	7 (50)	3 (30)	3 (17)	5 (45)	7 (47)	1 (33)	2 (40)	33 (38)
ROP ≥ 3, *n* (%)	2 (15)	3 (21)	0 (0)	1 (6)	0 (0)	2 (13)	0 (0)	0 (0)	8 (9)
IVH gr 3 or 4, *n* (%)	0 (0)	0 (0)	0 (0)	2 (11)	1 (9)	3 (20)	1 (33)	0 (0)	7 (8)
PVL, *n* (%)	0 (0)	3 (21)	0 (0)	1 (6)	2 (18)	1 (7)	0 (0)	2 (40)	9 (10)
Treated with indomethacin, *n* (%)	5 (38)	8 (57)	3 (30)	7 (39)	4 (36)	7 (47)	2 (67)	3 (60)	39 (44)
Surgical ligation for patent ductus, *n* (%)	3 (23)	5 (36)	0 (0)	0 (0)	1 (9)	3 (20)	1 (33)	1 (20)	14 (16)
NEC, *n* (%)	0 (0)	2 (14)	0 (0)	2 (11)	0 (0)	2 (13)	0 (0)	1 (20)	7 (8)
Surgery for NEC, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	1 (20)	2 (2)
Episodes with antibiotics, *n* (%)									
No antibiotics	5 (38)	3 (21)	2 (20)	4 (22)	0 (0)	2 (13)	0 (0)	0 (0)	16 (18)
1 or 2 episodes	6 (46)	8 (57)	7 (70)	12 (67)	9 (82)	10 (67)	2 (67)	4 (80)	58 (65)
>2 episodes	1 (8)	3 (21)	1 (10)	2 (11)	2 (18)	2 (13)	1 (33)	1 (20)	13 (15)
Duration of hospital stay, days mean ± SD	86.2 ± 22.7	99.4 ± 40.8	76.4 ± 15.8	88.4 ± 26.7	90.1 ± 26.2	88.3 ± 24.4	96.0 ± 10.5	91.0 ± 48.0	89.1 ± 28.3

pma, post-menstrual age.

Table 3. Neurodevelopmental Outcomes in the Study Arms

	Placebo n=*13*	*Iodine* n=*14*	*Bolus 4 μg/kg per d* n=*10*	*Continuous 4 μg/kg per d* n=*18*	*Bolus 8 μg/kg per d* n=*11*	*Continuous 8 μg/kg per d* n=*15*	*Bolus 16 μg/kg per d* n=*3*	*Continuous 16 μg/kg per d* n=*5*	*Total* n=*89*
Corrected age at assessment, months, mean ± SD	37.9 ± 5.9	39.2 ± 6.0	38 ± 2.2	38.9 ± 4.4	37.0 ± 4.1	37.4 ± 3.4	37 ± 5.3	34 ± 2.3	37.9 ± 4.5
Cerebral paresis, *n* (%)	1 (8)	1 (7)	0 (0)	3 (17)	2 (18)	1 (7)	0 (0)	0 (0)	8 (9)
Gross Motor Function Classification System, *n* (%)									
Level 1	1 (8)	0 (0)	0 (0)	2 (11)	0 (0)	1 (7)	0 (0)	0 (0)	4 (5)
Level 2	0 (0)	0 (0)	0 (0)	0 (0)	2 (18)	0 (0)	0 (0)	0 (0)	2 (2)
Level 3	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Level 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Level 5	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Bayley-III cognitive scaled score, mean ± SD	11.1 ± 2.5 *n*=11	9.2 ± 2.2 *n*=11	8.9 ± 0.8 *n*=8	9.8 ± 2.9 *n*=16	10.1 ± 2.4 *n*=9	9.4 ± 1.6 *n*=14	11.0 *n*=1	11.3 ± 1.5 *n*=3	9.8 ± 2.3 *n*=73
Bayley-III cognitive composite score, mean ± SD	105.5 ± 12.3 *n*=11	95.9 ± 10.9 *n*=11	94.4 ± 4.2 *n*=8	99.1 ± 14.7 *n*=16	100.6 ± 11.8 *n*=9	96.8 ± 8.0 *n*=14	105.0 *n*=1	106.7 ± 7.6 *n*=3	99.2 ± 11.3 *n*=73
Cognitive delay, *n* (%)									
No delay	11 (85)	8 (57)	5 (50)	12 (67)	8 (73)	11 (73)	1 (33)	3 (60)	59 (66)
Mild delay	0 (0)	4 (29)	5 (50)	5 (28)	3 (27)	3 (20)	0 (0)	0 (0)	20 (22)
Moderate delay	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Severe delay	1 (8)	2 (14)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	4 (4)
Missing	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (67)	2 (40)	5 (6)
Bayley-III fine motor scaled score, mean ± SD	11.8 ± 2.4 *n*=11	11.2 ± 1.3 *n*=11	11.3 ± 1.4 *n*=9	11.1 ± 2.4 *n*=16	10.8 ± 2.9 *n*=9	10.4 ± 2.4 *n*=14	10.0 *n*=1	11.7 ± 1.5 *n*=3	11.1 ± 2.2 *n*=74
Bayley-III gross motor scaled score, mean ± SD	11.0 ± 2.8 *n*=11	8.9 ± 1.8 *n*=11	8.7 ± 1.7 *n*=9	9.1 ± 4.0 *n*=16	9.4 ± 2.6 *n*=9	8.7 ± 2.5 *n*=14	7.0 *n*=1	10.0 ± 1.7 *n*=3	9.3 ± 2.8 *n*=74

Table 4. Adverse Outcome per Study Arm

	Placebo	*Iodine*	*Bolus 4 μg/kg*	*Continuous 4 μg/kg*	*Bolus 8 μg/kg*	*Continuous 8 μg/kg*	*Bolus 16 μg/kg*	*Continuous 16 μg/kg*	*Total group*
Total in study, *n*	28	25	24	27	20	27	7	8	166
3 year follow-up not done, *n*	10	7	12	5	3	6	1	1	45
3 year outcome known, *n*	18	18	12	22	17	21	6	7	121
Outcome at age 3 years									
Neonatal death, *n*	5	4	2	4	6	6	3	2	32
Abnormal development, *n*	1	2	0	2	2	1	0	0	8
Death or abnormal development*, %	33%	33%	17%	27%	47%	33%	50%	29%	33%

*Abnormal development: moderate or severe cognitive delay in development and/or cerebral paresis and Gross Motor Function Classification System ≥2.

direction of all differences and their lack of significance were much the same as in the study group as a whole.

In the last comparisons, Table 4 summarizes results of abnormal outcomes in the eight study arms. There were no statistically significant differences across treatment arms. If divided into groups of combined dosage (no hormone supplementation vs. 4 vs. 8 vs. 16 μg T4), adverse outcome was lowest, but not statistically so, in the combined 4 μg arms at only 24%, and highest in the combined 8 μg arms at 39% of subjects. Adverse outcome occurred in 33% of subjects in the arms that did not receive T4, and in 38% in the 16 μg arms. Use of nonparametric tests did not change the significance of any test result reported here.

Discussion

This study reports on neurodevelopmental outcome at age three in 89 infants born at less than 28 weeks gestational age, i.e. 66% of all surviving subjects that consented for a phase 1 trial on different treatment regimens for THOP (15). In 2001, the Amsterdam team of this international collaborative group reported from an earlier trial, that at 5 years of age, 29 infants born at less than 28 weeks gestational age who were in the T4 treatment arm [(8 μg/(kg·d)] had improved neuromotor outcome compared with 31 placebo infants, while cognitive outcome tended to be better only in T4 treated infants born at less than 27 weeks' gestation (12). On the other hand, no improvement or even worse neurodevelopment was found for T4-treated infants born beyond 28 weeks' gestation. This interaction with gestational age was based on post-hoc sub group analyses of a trial whose overall finding was null. We concluded that these uncertain results needed further evaluation in a new randomized controlled trial. The current phase 1 trial was undertaken to set up such a trial and had as primary aim to find an optimal dosing regimen. The trial was powered for detecting differences in FT4 concentrations across the six study arms: placebo, iodine, and two 4 and 8 μg/(kg·d) treatment arms. However, because a protocol violation resulted in a dosing error at one of the three study sites, two additional study arms were created that provided a third dosing range with a relatively high T4 dose of 16 μg/(kg·d). Neurodevelopmental follow-up was not part of the original study design. Nevertheless, the current paper shows data on neurodevelopmental outcomes in the largest T4 supplemented patient group less than 28 weeks gestation to date (12,19).

No differences in cognitive, motor, and neurological development by study arm were found in the survivors, nor were any adverse outcomes (including death) found by study arm among all infants randomized. This absence of difference was true for the comparison of all eight study arms with each other, for the comparison of three arms grouped by mode of administration (bolus and continuous T4 by dose level) with each other and with the placebo/iodine arms, as well as for the comparison of all T4 recipients with all nonrecipients. However, attrition was substantial, with outcome data available for 66% of the survivors.

In general, the neurodevelopmental outcome of the 89 infants in our study was good, with only 9% having CP, and only 2% having severe forms of CP. This is consistent with outcome data reported in other international cohorts of infants born after a similar gestational age without T4 supplementation. The mean cognitive score was 99. This perhaps surprisingly high score was also found by others in similar patient groups when using the third version of the Bayley scale. Healthy term controls are reported to have a mean score of 110 (20). Although the Bayley-III scale underestimates developmental delay, the same test was used in all participating children, and thus we believe it is suitable for intergroup comparisons. Although at first glance these outcomes appeared to be better in the placebo arms, the frequency of adverse outcome was lowest in the 4 μg arms, highest in the bolus 16 μg arm, and intermediate in the placebo and iodine arm. Death, and not abnormal development, formed the largest part of the composite adverse outcomes measure in all study arms. None of these differences was statistically significant, although the highest death rate was seen in the 16 μg groups, and the lowest adverse outcome rate was seen in the combined 4 μg groups. In short, no indication of long term neurological benefit, nor of harm, was found by administering T4 in dosages from 4 μg/(kg·d) to a relatively high dosage T4 of 16 μg/(kg·d), as inadvertently occurred during our trial.

Our results, therefore, support the recommendation to use thyroid hormone for THOP only in the context of a clinical trial.

Our results can also be viewed as a basis for future research. This trial, like other thyroid hormone trials with data on neurodevelopment, selected infants for study on the basis of gestational age at birth. It might be advisable to select infants for future trials on the basis of thyroid hormone levels. Lower levels of plasma (F)T4 are found especially in preterm

infants with respiratory and infectious disease and in those receiving dexamethasone or dopamine (9,21). Another possibility is to treat preterm infants with neurologic injury such as intraventricular hemorrhage or white matter damage. Thyroid hormone may ameliorate the effects of loss of myelination that is associated with these types of neurologic injury (22,23).

(F)T4 concentrations are only transiently low in preterm infants. It might be that thyroid hormone metabolism readily adapts and that at a cellular level, sufficient T3 is available for normal neuronal development, due to increased T4 to T3 conversion in astrocytes (24). In that case, the serum biochemical observations are without clinical consequences. Balanced against this are large observational studies in which more adverse neurodevelopmental outcome in premature infants was found with the lowest levels of thyroid hormone early in neonatal life (10,11).

We found that FT4 levels in the placebo group were fairly stable over the eight week study period (15). Total T4 is bound to TBG and varies more widely than FT4 with postnatal maturation and with severity of disease. It is possible that associations between low T4 and neurodevelopment are more related to factors associated with disease than to insufficient thyroid hormone (9,12). There are very few reports on associations between neonatal FT4 and neurodevelopment, although we found mental outcome at age two years and motor outcome at age five years to be associated with low FT4 as measured by radioimmunoassay (12). Apart from the method, the problem of high free fatty acids due to parenteral nutrition and high heparin due to use of indwelling catheters in very preterm infants will always remain an issue for optimal FT4 measurement.

The limitations of our outcome report are evident. Although there was a protocol for neurodevelopmental assessments, no training sessions were planned nor quality checks done, as this was not an a priori goal of the phase 1 pharmacological trial. Nevertheless, follow-up was carried out by trained professionals masked to the treatment arm in all institutions. Secondly, follow-up was not complete for the cohort and was not evenly distributed between the three enrollment centers. In addition, the sickest neonates tended to be overrepresented in the treatment arm that did not achieve the best follow-up. Thirdly, the various arms were small and were divided between seven different drug treatment protocols and a placebo arm, forcing the comparisons to be constructed in a post hoc manner by combining various iterations of similarities between arms; none were properly powered for a valid outcome conclusion. Power was only sufficient to rule out large differences between groups. Lastly, despite the wide acceptance of the BSITD III as a clinical instrument, its actual scores are not very sensitive to find between-group distinctions.

Our results represent the largest series of thyroid hormone supplemented infants in infants born at less than 28 weeks gestation since 1999, but they do not resolve the issue of whether supplementing infants with an optimum dose of T4 and creating biochemical euthyroidism improves neurodevelopmental outcome. Further trials are warranted.

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Clinical Trials.gov Registry was not required, because (i) this is a phase 1 trial, Public Health Law 110-85, Title VII as defined in Section 312.21 of Title 21, Code of Federal Regulations; Grant NS45109 Title: Phase 1 trial of thyroid hormone in prematures; (ii) enrollment began April 2005 and was completed March 2007, eclipsing the mandated start date of July 2007; and (iii) it is a NINDS sponsored trial with information already registered in a public domain.

Author Disclosure Statement

The authors declare that no competing financial interests exist.

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