Journal of Perinatology (2017) 00, 1–4

www.nature.com/jp

ORIGINAL ARTICLE

Effect of L-thyroxine supplementation on very low birth weight infants with transient hypothyroxinemia of prematurity at 3 years of age

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OBJECTIVE: To evaluate the effects of levothyroxine (L-T4) supplementation on growth and neurodevelopmental outcomes at 3 years of age in very low birth weight (VLBW) infants with transient hypothyroxinemia of prematurity (THOP).
STUDY DESIGN: VLBW infants with plasma thyroid-stimulating hormone concentrations $< 10\ \mathrm{mIU\ l^{-1}}$ and free thyroxine concentrations $< 0.8\ \mathrm{ng\ dl^{-1}}$ were defined as having THOP and randomly assigned to the Treated (20 infants) or Untreated (31 infants) group. The Treated group received L-T4 at a dose of $5\ \mu\mathrm{g\ kg^{-1}\ day^{-1}}$. Growth and neurodevelopmental outcomes at 3 years of age were compared between the two groups.
RESULTS: There were no significant differences in body length, body weight or head circumference mean s.d. scores or in neurodevelopmental outcomes between the two groups.
CONCLUSION: L-T4 supplementation in VLBW infants with THOP demonstrated no beneficial effect at 3 years of age.

Journal of Perinatology advance online publication, 26 January 2017; doi:10.1038/jp.2016.266

INTRODUCTION

Thyroid hormones are known to have an important role in the normal development of the central nervous system during the fetal and early neonatal periods.[1–5] Thyroid hormones are also essential for normal somatic growth,[6] and low thyroid hormone concentrations are associated with poor growth and neurodevelopmental outcomes.[7–11] Preterm infants often have transient hypothyroxinemia of prematurity (THOP).[12–14] This condition is characterized by transient reduction in thyroid hormones lasting 6 − 8 weeks without elevation of thyroid-stimulating hormone (TSH) concentration and is more common with increasing degrees of prematurity.[14] The effects of THOP on neurodevelopmental outcomes are controversial.[1–4,12–16] If THOP is harmful for preterm infants, levothyroxine (L-T4) supplementation may have beneficial effects against growth and neurodevelopmental outcomes. However, whether L-T4 supplementation improves these outcomes in infants with THOP remains under debate.[1,2,5,7,17–20]

We previously reported that L-T4 supplementation in very low birth weight (VLBW) infants with THOP showed no beneficial effect at 18 months of corrected age.[20] However, the long-term effects of L-T4 supplementation on VLBW infants are unclear. In this study, we evaluated whether L-T4 supplementation improves growth and neurodevelopmental outcomes in VLBW infants with THOP at 3 years of age.

MATERIALS AND METHODS

Design

This study was planned as an unmasked, prospective, multi-center randomized clinical trial (CRT: UMIN000001953). It was conducted at the neonatal intensive care units of Tokyo Women's Medical University and the Metropolitan Bokutoh Hospital, belonging to the Tokyo Metropolitan Neonatal Research Group. The study design was approved by the Committee of Medical Ethics in each hospital.

Subjects

VLBW infants born between October 2005 and March 2011and treated in the two neonatal intensive care units were eligible for this study. Plasma TSH and FT4 concentrations between 2 and 4 weeks of age were measured using chemiluminescent enzyme immunoassay kits. Inclusion and exclusion criteria were previously reported.[20] Briefly, VLBW infants were enrolled if they demonstrated both TSH concentration $< 10\ \mathrm{mIU\ l^{-1}}$ and FT4 concentration $< 0.8\ \mathrm{ng\ dl^{-1}}$. Exclusion criteria were severe congenital malformations, chromosomal anomalies and maternal thyroid disease.

Randomization and assignment

Details of randomization and group assignment are described in our previous report.[20] After informed consent was obtained from at least one parent, the infants were randomly assigned to the Treated or Untreated group. When informed consent could not be obtained, the infants were assigned to the Untreated group if the parents approved their inclusion in the study analysis. Therefore, the number of patients differed between the two groups.

Intervention

Infants in the Treated group received L-T4 ($5\ \mu\mathrm{g\ kg^{-1}}$ once per day) approximately up to the expected date of confinement (EDC). Plasma concentrations of TSH and FT4 were measured every 2 weeks up to the EDC in both groups. If FT4 concentration was $> 2.0\ \mathrm{ng\ dl^{-1}}$, the L-T4 dose was halved. Supplementation was stopped if FT4 concentration persistently exceeded $2.0\ \mathrm{ng\ dl^{-1}}$ in spite of decreasing the L-T4 dose. When the study infants reached EDC, L-T4 supplementation was stopped. If FT4 concentration was $< 0.8\ \mathrm{ng\ ml^{-1}}$ at 1 week after stopping the medication, L-T4 treatment ($5\ \mu\mathrm{g\ kg^{-1}\ day^{-1}}$) was resumed. Infants in the Untreated group did not receive L-T4 during the study period.

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Received 26 August 2016; revised 26 November 2016; accepted 13 December 2016

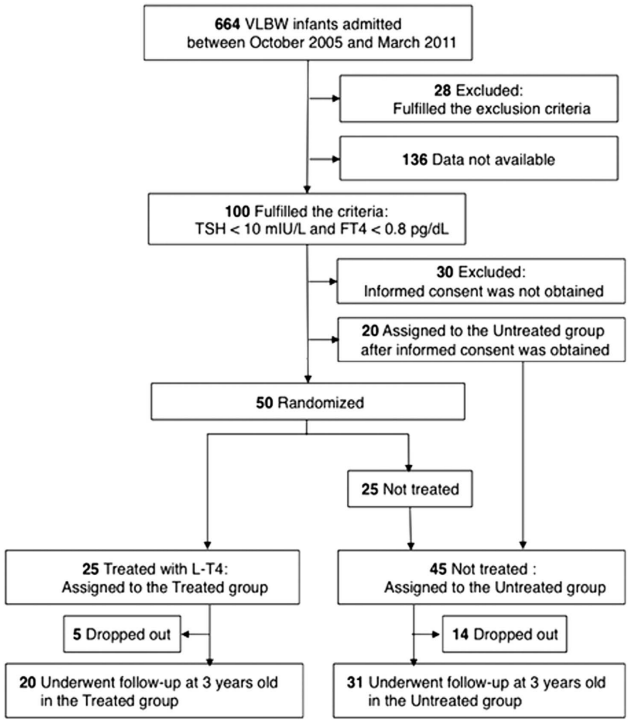

Figure 1. Flowchart of the study population. L-T4, levothyroxine; TSH, thyroid-stimulating hormone; VLBW, very low birth weight.

Outcome measures

We examined the clinical records of eligible infants and compared the following prenatal and postnatal clinical characteristics between the two groups: prenatal incidences of pregnancy-induced hypertension, histological chorioamnionitis, use of betamethasone, non-reassuring fetal status and cesarean section; perinatal factors of gestational weeks, birth weight, sex and Apgar scores at birth; and postnatal incidences of respiratory distress syndrome, patent ductus arteriosus, grade 3 or 4 cerebral hemorrhage, necrotizing enterocolitis, late-onset circulatory collapse, periventricular leukomalacia, sepsis, retinopathy of prematurity and chronic lung disease at 36 weeks. All clinical factors are defined in our previous report.[20]

To evaluate the effects of L-T4 supplementation on growth, we compared mean *Z*-scores of length, body weight and head circumference in the study subjects at 3 years of age between the two groups. To evaluate the effects of L-T4 supplementation on neurodevelopmental outcomes, we compared their developmental quotient (DQ) using the Kyoto Scale for Psychological Development (KSPD) at the same time,[21,22] along with incidences of cerebral palsy (CP), severe visual impairment and severe hearing impairment. CP was defined as non-progressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture.[23] Severe visual impairment and severe hearing impairment were defined as previously reported.[20] Follow-up was performed according to the protocol of the Japanese Society for Follow-up Study of High-risk Infants.[21]

Sample size calculation

We assumed that treatment with L-T4 would improve DQ in the treated group by 15 points, with an s.d. of 15.[10] Sample size was calculated as at least 20 infants in each arm, at 80% power and $P < 0.05$.

Statistical analysis

Clinical characteristics of the study subjects were compared using unpaired Student's *t* tests or Mann–Whitney *U*-tests for continuous data and chi-square analysis or Fisher's exact test for categorical data. Differences with *P*-values < 0.05 were considered significant. Statistical analyses were performed using the JMP Pro software version 12.0 for Macintosh (SAS Institute, Cary, NC, USA).

RESULTS

Study population

Figure 1 shows the flowchart of the study population. A total of 664 VLBW infants were admitted to the two neonatal intensive care units during the study period. Of these, 28 infants were excluded because they fulfilled the exclusion criteria, and 136 were excluded owing to the absence of TSH and FT4 data. Of the remaining 500 infants, 100 (20%) fulfilled the inclusion criteria. Among them, the parents of 50 infants consented to study randomization, and the parents of another 20 infants approved assignment into the Untreated group. As a result, 25 and 45 infants were assigned to the Treated and Untreated groups, respectively. During the study period, 5 infants in the Treated group and 14 in the Untreated group dropped out. Among the 5 infants in the treated group, 4 moved, and 1 was lost to follow-up. Among the 14 Untreated infants, 8 moved, and 6 were lost to follow-up. Finally, 20 infants in the Treated group and 31 in the Untreated group underwent follow-up at 3 years of age. Among the Treated group, KSPD was not performed in one infant at that time owing to severe athetoid-type CP that prevented KSPD evaluation.

Comparison of clinical characteristics

The Treated and Untreated groups demonstrated no significant differences in prenatal or perinatal factors. Among postnatal factors, the incidences of clinical characteristics that can affect neurodevelopmental outcomes, such as intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia and chronic lung disease at 36 weeks, did not significantly differ with the exception of the incidence of respiratory distress syndrome (Treated group, 95% vs Untreated group, 68%, $P = 0.02$). Overall, baseline clinical characteristics of the infants in the two groups were similar (Supplementary Table).

Safety of L-T4 supplementation

No infants in the Treated group demonstrated L-T4 > 2.0 ng dl^{-1} during supplementation or any side effects of the medicine. No infants in the Treated group demonstrated FT4 concentration < 0.8 ng ml^{-1} after stopping L-T4 supplementation at the EDC. Consequently, no infants resumed L-T4 supplementation throughout the study period.

Comparison of longitudinal changes in TSH and FT4 concentrations

Longitudinal changes of TSH and FT4 concentrations until EDC were similar to those in our previous report.[19] Briefly, compared with infants in the Untreated group, those in the Treated group showed a significantly lower mean plasma concentration of TSH for approximately 4 weeks after starting L-T4 supplementation. By contrast, the time course of mean plasma FT4 concentration did not significantly differ between the two groups. Mean plasma FT4 concentration did not significantly differ between the groups (Treated, 0.63 ± 0.03 ng dl^{-1} vs Untreated, 0.58 ± 0.03 ng dl^{-1}) before starting L-T4 supplementation, gradually increased up to 7–8-week postnatal age in both groups and then maintained at 1.1–1.2 ng dl^{-1} until the EDC. Based on these results, longitudinal changes in TSH and FT4 concentrations in the study subjects were compatible with states of THOP (Supplementary Figure).

Comparison of growth and neurodevelopmental outcomes at 3 years of age

Table 1 shows the mean *Z*-scores of body length, body weight and head circumference at 3 years of age in the two groups, which did not significantly differ between the groups.

Table 1. Comparison of body length, weight and head circumference at 3 years

	Treated group (n = *20*)	*Untreated group* (n = *31*)	P-*value*
Body length (*Z*-score)	−1.16 ± 0.95	−1.19 ± 0.98	0.93
Body weight (*Z*-score)	−0.85 ± 1.05	−1.00 ± 1.15	0.62
Head circumference (*Z*-score)	−0.48 ± 0.82	−0.71 ± 1.30	0.49

Data are expressed as mean ± s.d.

Table 2. Comparison of neurodevelopmental outcome at 3 years

	Treated group (n = *20*)	*Untreated group* (n = *31*)	P-*value*
KSPD overall DQ[a]	85 ± 15	89 ± 17	0.34
P–M DQ[a]	92 ± 17	96 ± 18	0.47
C–A DQ[a]	85 ± 13	88 ± 19	0.54
L–S DQ[a]	82 ± 19	88 ± 21	0.30
KSPD overall DQ < 70 (%)[a]	3 (16)	3 (10)	0.85
Cerebral palsy (%)	1 (5)	0 (0)	0.39
Severe visual impairment (%)	1 (5)	3 (10)	0.49
Severe hearing impairment (%)	1 (0)	0 (0)	–

Abbreviations: C–A, cognitive–adaptive; DQ, developmental quotient; KSPD, Kyoto Scale for Psychological Development; L–S, language–social; P–M, postural–motor. KSPD was not performed in one subject in the Treated group owing to severe athetoid cerebral palsy. [a]Each DQ value was evaluated using the KSPD.

Among neurodevelopmental outcomes, there were no significant differences in overall, postural–motor, cognitive–adaptive and language–social DQs on the KSPD or in the incidence of developmental delay, defined as overall DQ < 70, between the two groups. The CP, severe visual impairment and hearing impairment incidences were also similar (Table 2).

DISCUSSION

We previously reported that L-T4 supplementation in VLBW infants with THOP demonstrated no beneficial effects to growth and neurodevelopmental outcomes at 18 months corrected age.[20] We continued follow-up of this cohort to evaluate effects of L-T4 supplementation at 3 years of age and obtained similar results, namely, that L-T4 supplementation had no obvious effects on growth or neurodevelopmental outcomes. These results are unsurprising because the time course of mean plasma FT4 concentration showed no significant differences between the Treated and Untreated groups throughout the L-T4 supplementation period. We administered 5 μg kg^{-1} of L-T4 to the Treated group, not 10 μg kg^{-1} day^{-1}, because it was recently reported that L-T4 supplementation may be related to the development of late-onset circulatory collapse, which is thought to be associated with complications of postnatal periventricular leukomalacia and CP in VLBW infants.[24] If more or higher doses of L-T4 had been administered, the results might have differed. Several previous reports have claimed that timing of intravenous thyroxine administration should be within 1 week of age.[1,5,19] In this study, we started L-T4 by oral administration at 2 weeks of age in the Treated group, because enteral nutrition is usually established around 2 weeks of age in such subjects in our facilities. It is unclear whether the timing of initiating L-T4 administration affected the results.

The mean plasma TSH concentration was significantly lower in the Treated group at approximately 4 weeks after starting L-T4 supplementation, compared with the Untreated group. We cannot explain these results, because no infants in the Treated group showed clinical abnormalities during L-T4 supplementation. However, we believe that suppression of TSH concentrations in the Treated group indicates an effect of L-T4 supplementation on infants leading to abnormal physiological conditions. Further studies involving measurement of triiodothyronine or free triiodothyronine concentration may clarify the meaning of this TSH suppression. Although low thyroid hormone concentrations are associated with poor growth and neurodevelopmental outcomes,[7–11] it is debatable whether THOP negatively impacts these outcomes.[12–16] If THOP reflects normal physiological conditions, TSH suppression by L-T4 supplementation represent overtreatment. Therefore, routine use of L-T4 supplementation should be avoided in infants with THOP.

To date, no unified cutoff values of TSH and FT4 have been established to diagnose THOP. In this study, we used cutoff values of TSH < 10 μU ml^{-1} and FT4 < 0.8 ng dl^{-1}, on which basis 100 of 500 VLBW infants (20%) were diagnosed with THOP. Consistent with our study, THOP incidence has been previously estimated at approximately 20% of infants.[25,26] Therefore, the cutoff values appear acceptable to diagnose as THOP if TSH and FT4 concentrations are measured simultaneously in VLBW infants.

This study has several limitations. First, the sample size is small. Second, parental informed consent could not be obtained in many cases. Finally, the incidence of loss to follow-up was high, especially in the Untreated group, possibly because these infants did not receive any intervention. Therefore, our data may not represent the characteristics of all subjects in this study. Further studies with larger samples are required to ensure the need for medical interventions in such patients.

In conclusion, L-T4 supplementation at a dose of 5 μg kg^{-1} day^{-1} in VLBW infants with THOP had no beneficial effect on growth or neurodevelopmental outcomes at 3 years of age. Based on these results, routine use of L-T4 is not recommended in such patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank Cactus Communications for editing the medical English language of the manuscript.

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Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)