

Basal serum thyroxine level should guide initial thyroxine replacement dose in neonates with congenital hypothyroidism

Short title: Thyroxine dose in congenital hypothyroidism

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Abstract

Objective: Initial high-dose Na-L thyroxine (Na-LT₄) (10-15 µg/kg/day) replacement for primary congenital hypothyroidism (CH) is recommended in guidelines. However, high-dose Na-LT₄ has risks. In this study, we aimed to investigate normalizing effect of varying initial doses of Na-LT₄ on serum thyroid hormone levels.

Methods: Fifty-two patients were analyzed retrospectively. The patients were classified into mild (27/51.9%), moderate (11/21.1%) and severe (14/26.9%) CH with respect to initial free thyroxine (FT₄) levels. Time taken to achieve target hormone levels was compared within groups.

Results: Initial mean Na-LT₄ doses for mild, moderate and severe disease were 6.9±3.3, 9.4±2.2 and 10.2±2 µg/kg/day. Serum FT₄ levels reached the upper half of normal range (>1.32 ng/dL) in a median of 16, 13 and 16 days in patients with mild, moderate and severe CH with the mean time from initial treatment to first control visit 14.8 ± 6 days (range 1-36). There was no significant difference in terms of time to achieve target FT₄ hormone levels according to disease severity (p=0.478). Seven (25.9%), 8 (72.7%) and 8 (57.1%) patients experienced hyperthyroidism (serum FT₄ >1.94 ng/dL) in mild, moderate, severe CH groups in the first visit, respectively (p=0.016).

Conclusion: Not all patients diagnosed with CH require high-dose Na-LT₄. Initial dose of Na-LT₄ may be tailored based on pre-treatment thyroid hormone levels. Some patients with moderate and severe CH, experienced iatrogenic hyperthyroidism even though the dose was close to the lower limit of the recommended range in guidelines; suggesting lower initial doses and closer follow-up within the first week.

Keywords: Newborn screening, children, congenital hypothyroidism, Na-L thyroxine, dose

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Introduction

Congenital hypothyroidism (CH) is the most common endocrinological problem in newborns with an incidence of 1:2000-1:4000 and has a rising incidence as reported in recent studies (1,2). Thyroid hormones are essential for brain development, especially prenatal neuronal differentiation, migration and proliferation as well as postnatal myelination; thus delay in diagnosis and treatment of CH leads to irreversible brain damage and permanent neurodevelopmental defect (3,4).

Studies suggest that rapid normalization of thyroid hormones after birth, in infants with severe hypothyroidism may provide better cognitive outcomes (5). Therefore, guidelines for neonatal screening for CH recommend initial high-dose Na-L thyroxine (Na-LT₄) (10-15 µg/kg/day) replacement to normalize serum thyroid hormone levels rapidly in order to achieve better outcomes (6). The guidelines also recommend the first follow-up visit should take place 1-2 weeks after the onset of Na-LT₄ treatment. However significant developmental improvement could not be shown for mild to moderate hypothyroidism using higher doses. Furthermore, recent data suggests a risk of iatrogenic hyperthyroidism with its probable negative impact on behavior and attention in infants who are prescribed high initial doses (7-9). In consideration of these recent reports, the latest European Society for Pediatric Endocrinology consensus guideline suggested, for the first time, that the initial dose of Na-LT₄ may be titrated with respect to initial hormone levels and disease severity (10).

In the current study, we aimed to investigate the effect of varying initial doses of Na-LT₄ on serum thyroid hormone levels in neonates and infants with primary CH.

Methods

Patients with primary neonatal CH diagnosed at Hacettepe University Medical Faculty, Division of Pediatric Endocrinology between January 2009 and January 2013 were included in the study. Patients, with a serum free thyroxine (FT₄) lower than 0.93 ng/dL (normal range: 0.93-1.71 ng/dL) and thyroid stimulating hormone (TSH) higher than 10mIU/L (normal range: 0.27-4.2 mIU/L) were considered to be primary CH. Patients with a gestational age of < 37 weeks, history of severe underlying illness or central hypothyroidism, as well as those in whom treatment was delayed for 3 months were excluded from the study.

Patients' files were analyzed retrospectively to identify the etiology of CH and severity of hypothyroidism as determined by initial FT₄ levels, as well as doses of Na-LT₄, and hormonal follow-up. Patients were grouped with respect to etiology, severity of CH, and initial dose of thyroxine (low vs high). Etiological classification of the study group relied on imaging as well as re-evaluation of thyroid hormones at 3 years of age after cessation of treatment.

Groups

(i) Patients were categorized into two groups (a) patients with normal thyroid function after therapy withdrawal at 3 years of age were classified as transient CH; (b) patients with persistent hypothyroidism following cessation of therapy at 3 years of age were considered as permanent CH. Both groups were compared for the time to achieve target hormone levels from onset of treatment.

(ii) Patients were categorized into three groups according to pretreatment plasma FT₄ concentrations; severe CH (FT₄ ≤ 0.31 ng/dL), moderate CH (0.31 < FT₄ ≤ 0.62 ng/dL) and mild CH (FT₄ > 0.62 ng/dL). Mild, moderate and severe CH groups were compared for the time to reach target hormone levels from onset of treatment.

(iii) Patients were divided into two groups with respect to initial dose of Na-LT₄; those with an initial dose less than 10 µg/kg/day were defined as low-dose group, those with an initial dose more than 10 µg/kg/day were defined as high-dose group. Both groups were compared for the time to achieve target hormone levels from onset of treatment.

Hormone levels

Initial and follow-up thyroid hormone levels were extracted from medical records to analyze time to reach euthyroidism. Treatment targets were (1) to achieve upper half of normal range for serum FT₄ (>1.32 ng/dL), and (2) serum TSH <10 mIU/L. In most patients, records included serum FT₄ and TSH levels every 1-2 weeks for the first 2 months of life, then every 1-3 months until 12 months of age, and thereafter every 3 months; and more often in those with problems in compliance during follow-up, though due to the retrospective nature of the study the time intervals between visits were not homogeneous. Blood samples were obtained in the morning before Na-LT₄ administration.

Patients who experienced a serum FT₄ level lower than 0.93 ng/dL in the first visit were considered to be hypothyroid.

Dose management of Na-LT₄ was made on an individual basis by the primary endocrinologist. However, general approach in our department is tailoring the initial dose to pretreatment FT₄ levels.

This is a retrospective analysis of medical records. Serum FT₄ and TSH levels were measured by chemiluminescence method using IMMULITE 2000 System kits, Siemens, UK during the studied period. Intra- and inter-assay variation coefficients for TSH were 5.3% and <6.4% and they were <7.1% and <7.8% for free T₄, respectively.

Iatrogenic Hyperthyroidism

Serum FT₄ levels higher than 1.94 ng/dL in the first visit among transient/permanent CH, mild/moderate/severe CH, and low-dose/ high-dose initial therapy groups were analyzed.

This study was approved by Hacettepe University Medical Faculty Non-Invasive Clinical Research Ethics Committee (GO 13/406-24).

Statistical analysis

Statistical analysis was performed using the IBM SPSS 22.0 software (SPSS Inc., IL, USA). Numerical variables were summarized by mean± standard deviation or median (min-max) as appropriate. Normality of the numerical variables were determined by Shapiro-Wilks test. Because numerical variables in the dataset has skewed distribution, nonparametric Kruskal-Wallis and Mann-Whitney U test were used to compare independent groups (such as CH groups). Differences between groups in terms of categorical variables were examined by the Chi-square test or Fisher's exact test. p value less than 0.05 was considered statistically significant.

Results

Seventy-one patients with CH were extracted from hospital records within the time frame, 7 patients were excluded since the age at diagnosis was later than 45 days, 8 patients were excluded for incompliance leading to treatment failure to reach target serum levels. Furthermore, 4 patients with subclinical hypothyroidism with unknown cause (etiology was unknown at diagnosis, and serum FT₄ were normal however TSH levels were elevated after cessation of treatment at three years of age) were also excluded. The final study group consisted of 52 children. Twenty-three (44.2%) were girls and 29 (55.5%) were boys. Mean age at diagnosis and treatment was 20.6 ± 9.9 days (7-43); 28.8% of the parents were consanguineous.

Twenty-three (44.2%) patients had spot urinary iodine measurements, none of the results showed exposure to excessive iodine. Twenty-one (40.4%) mothers had spot urinary iodine measurements, which showed iodine sufficiency in 4 (19%) and deficiency in 17 (91%). Seven (41.2%) had mild (5-10 µg/dL), 7 (41.2%) moderate (2-5 µg/dL) and 3 (17.6%) severe (<2 µg/dL) iodine deficiency. Babies of ten mothers with iodine deficiency (58.8%) were in the transient CH group, whereas the remaining 7 (41.2%) were in the permanent CH group.

Mean serum levels of FT₄ and TSH at diagnosis were 0.75 ± 0.48 ng/dL and 70.6 ± 48.8 mIU/L, respectively. Mean initial Na-LT₄ dose was 8.4 ± 3.1 µg/kg/day. The mean time from initial treatment to first control visit was 14.8 ± 6 days (1-36).

The median time for FT₄ level to rise above 1.32 ng/dL was 16 (1-100) days, and the median time for TSH level to go below 10 mIU/L was 17 (1-88) days.

None of the patients experienced hypothyroidism in the first visit; 48 patients (92.3%) achieved target serum FT₄ levels, only 4 children (7.7%) had FT₄ levels under 1.32 ng/dL (0.99-1.31 ng/dL). Three of 4 achieved target serum FT₄ levels in the second visit (12-31 days), one of them had initial low-dose Na-LT₄ (7.14 µg/kg/day), the other two had initial high-dose Na-LT₄ (10.53; 12.2 µg/kg/day). The remaining one achieved target serum FT₄ levels in the third visit (100th day), he had initial low-dose Na-LT₄ (7.35 µg/kg/day).

Disease Severity

Twenty-seven (51.9%) patients had mild, 11 (21.1%) moderate, and 14 (26.9%) severe CH. The mean initial Na-LT₄ dose to mild, moderate and severe groups were 6.9 ± 3.3; 9.4 ± 2.2; 10.2 ± 2 µg/kg/day, respectively. The initial treatment dose of the mild group was lower than that of moderate and severe groups (p<0.001). High-dose initial Na-LT₄ treatment was initiated 4 (14.8%); 6 (56.5%); 8 (57.1%) patients in the mild, moderate and severe groups, respectively (p=0.006).

The median time for patients to reach target serum levels of FT₄ (>1.32 ng/dL) was 16 (3-49), 13 (7-100) and 16 (1-36) days for mild, moderate and severe groups, respectively (p=0.478). The median time for patients to achieve target serum levels of TSH (<10 mIU/L) was 16 (5-31), 15(8-27) and 30 (1-88) in mild, moderate and severe groups, respectively (p=0.003).

Permanent versus Transient Congenital Hypothyroidism

Twenty-four (46.1%) patients had permanent CH, and 28 (53.9%) had transient CH. In the permanent CH group, 13 patients had dysgenesis, 11 had dysmorphogenesis. Of 13 patients with thyroid dysgenesis, 3 (23.1%) had agenesis, 8 (61.5%) had ectopy, 1 had (7.7%) hypoplasia, and 1 (7.7%) had hemiagenesis.

The mean initial Na-LT₄ dose was 9.8±2.8 and 7.1±2.9 µg/kg/day in patients with permanent and transient CH, respectively. The initial dose was significantly higher in patients with permanent congenital hypothyroidism than the transient group (p=0.003) (Table 1). Twelve patients (50%) in permanent, and 6 patients (21.4%) in transient CH group underwent high-dose initial Na-LT₄ therapy (p=0.031).

Thirteen (54.2%), 7 (29.2%) and 4 patients (16.7%) with severe, moderate and mild CH, respectively, were in the permanent CH group; on the other hand, 1(3.6%) child with severe CH, 4 (14.3%) and 23 (82.1%) children with moderate and mild CH, respectively, were in the transient CH group. While the patients with severe CH were mainly in the permanent group, the patients with mild CH were principally in the transient group (p< 0.001).

The median time for serum levels of FT₄ to rise above 1.32 ng/dL was 15.5 (1-49) and 16 (3-100) in patients with permanent and transient CH, respectively (p=0.927). The median time for serum levels of TSH to decrease below 10 mIU/L was 18.5 (1-88) and 16 (5-31) in patients with permanent and transient CH, respectively (p=0.079). No statistically significant difference was found between the two groups.

Low versus High Initial Dose of Na-LT₄

The mean initial Na-LT₄ dose was 11.8 ±1.4 µg/kg/day for the patients in the high dose (n=18, 34.6%) and 6.4 ±2.1 µg/kg/day for the low dose groups (n=34, 65.4%) (Table 2).

The median time for FT₄ level to increase above 1.32 ng/dL was 12.5 (1-49) days for patients in the high-dose, and 16 (3-100) days for patients in the low-dose group (p=0.081). The median time for TSH level to decrease below 10 mIU/L was 17 (1-83) days for patients in the high-dose, and 17 (5-88) days for patients in the low-dose group. (p=0.664). No statistically significant difference was found between the groups.

Overtreatment

Analysis of FT₄ levels revealed that 23 (44.2%) patients experienced serum levels of FT₄ >1.94 ng/dL in the first visit. None of them showed any signs/symptoms of hyperthyroidism

We analyzed the particular effect of high initial doses on FT₄ in the first visit. The mean time from initial treatment to first control visit was 11.7 ± 5.1 and 16.4±6 days in high-dose, and low-dose treatment groups, respectively (p=0.005). We compared high-dose, and low-dose initial treatment in terms of iatrogenic hyperthyroidism during the course of reaching treatment goals; 10 (55.5%) and 13 (38.2%) patients experienced serum levels of FT₄ >1.94 ng/dL in high-dose and low-dose treatment groups in the first visit, respectively (p=0.36).

We compared mild, moderate and severe CH groups in terms of iatrogenic hyperthyroidism in the first visit. The mean time from initial treatment to first control visit was 14.9 ±7.7, 13.4 ±5.8 and 15.3±5.3 days in mild, moderate, and severe CH groups, respectively (p=0.33). Seven (25.9%), 8 (72.7%) and 8 (57.1%) patients experienced serum levels of FT₄ >1.94 ng/dL in mild, moderate, and severe CH groups in the first visit, respectively (p=0.016)

We compared permanent and transient CH in terms of iatrogenic hyperthyroidism in the first visit. The mean time from initial treatment to first control visit was 14.5±6.6 and 15.1±5.1 days in permanent and transient groups, respectively (p=0.47).

Fifteen (62.5%) and 8 (28.6%) patients experienced serum levels of FT₄ >1.94 ng/dL in permanent and transient CH in the first visit, respectively (p=0.03).

Discussion

Congenital hypothyroidism is one of the most common treatable cause of intellectual disability. Studies have shown that thyroid hormones have a crucial role in the appropriate formation of neuronal architecture as well as differentiation (11,12). High initial doses of Na-LT₄ (10-15 µg/kg/day) are recommended for rapid normalization of thyroid hormones for all infants irrespective of severity and cause of CH; though few studies have shown lower doses may have also similar success with less risk of overtreatment (6,7,13,14). Supraphysiological levels of FT₄ may result in premature craniosynostosis, behavioral problems, attention impairment, furthermore, may have negative effect on IQ at adolescence as one Dutch study has shown (13-16). Although the importance of early detection and effective treatment of CH is beyond dispute, there are some controversies in standard high dose Na-LT₄ (17,18).

Soliman et al. have reported that around one fourth of 45 patients who received high dose Na-LT₄ (15 µg/kg/ day) as initial therapy experienced hyperthyroxinemia during follow-up (19). Craven and Frank has shown high initial Na-LT₄ (>12.5 µg/kg/day) may lead to hyperthyroxinemia that required dose reduction in more than half of the patients during follow-up. They suggested narrower range for dosing would avoid over-treatment (7). Furthermore, limited information is available about how a targeted dosing strategy compares to initial high dosing (10-15 µg/kg/day) to achieve target serum FT₄ and TSH levels. We aimed to provide some data on this issue, and we have evaluated patients diagnosed with primary CH and investigated the influence of different initial doses of Na-LT₄ on thyroid hormone levels as well as the time to achieve target levels. We also analyzed the time to achieve target hormone levels from onset of treatment in perspective of etiologies and disease severity. Furthermore, we analyzed patients who developed hyperthyroidism during initial hormone treatment, and its relation to initial doses, disease severity and whether CH is permanent or transient.

Mathai et al. has questioned single initial Na-LT₄ dose for all CH patients and reviewed variable initial dose strategy in permanent CH (20). In their study, Na-LT₄ treatment was given in 10, 12 and 15µg/kg/day doses for dysmorphogenesis, ectopia and athyreosis, respectively. They showed these doses succeeded in normalizing serum FT₄ within 14 days. They also showed that lower doses (9.98±3.19 µg/kg/day) of Na-LT₄ enabled target serum FT₄ levels in cases with permanent CH within a median of 16 days. Bakker et al. has studied 30 CH neonates who were treated with initial daily T₄ dosages ranging from 4.8 to 11.1 µg/kg and found no correlation between the initial dose (whether high or low) and the time for normalization

of plasma FT₄ levels (21). The mean initial Na-LT₄ dose was 8.4 ± 3.1 µg/kg/day in the current study, moreover both low (6.4 ± 2.1 µg/kg/day) and high (11.8 ± 1.4 µg/kg/day) dose groups achieved target serum FT₄ and TSH levels within similar time frames. Tuhan et al has studied effect of three different initial Na-LT₄ doses (6-9.9 µg/kg/day, 10-11.9 µg/kg/day and 12-17 µg/kg/day) on serum TSH levels in the first month, and reported no statistical difference between groups (22). In the current study, varying initial doses of Na-LT₄ (6.9±3.3; 9.4±2.2; 10.2±2 µg/kg/day) in mild, moderate, severe CH groups achieved target FT₄ serum concentrations within similar time-frame, suggesting titration of initial Na-LT₄ doses to initial hormone levels may be a valid strategy for effective treatment. We showed comparable efficacy of lower doses to achieve target serum FT₄ levels in the mildly and moderately affected subgroups, against severe hypothyroidism treated with high doses. On the other hand, severe CH group achieved target TSH serum concentrations in a longer time than mild and moderate groups (30 vs 16,15 days respectively) in our study. Persistent high serum levels of TSH in early phase of treatment has been reported, furthermore FT₄ concentration is considered more helpful in determining T₄ supplementation doses in this specific time span in some studies (21,23). Our results suggest impairment of hypothalamic-pituitary-thyroid axis negative feedback control may be more prominent in severe CH subgroup similar to Hanukoglu and colleagues had shown (24). Our cohort has an increased percentage of transient CH (53.9%) like the current published French study in which more than half of the study population had transient CH (25). The increased percentage of transient CH in these studies may be attributed to iodine deficiency in both countries (25,26) Spot urinary iodine measurements of the mothers in the current study also showed that iodine deficiency is still a problem in the maternal age group. A good number of patients in both our cohort and French study presented with mild hypothyroidism at the time of diagnosis and received lower initial doses of Na-LT₄ in comparison to guidelines. We consider this special subgroup of patients with mild, and usually transient hypothyroidism may be related to iodine deficiency rather than primary congenital defects of the thyroid gland or hormone genesis, and they may need lower initial Na-LT₄ replacement doses. Furthermore, they may have an increased risk of overtreatment with standard high dose therapy.

Indeed, hyperthyroidism is an issue in high-dose treatment. Tuhan et al. studied 71 children with CH, and showed 43.1% of patients were overtreated, furthermore 5 of them experienced clinical signs of hyperthyroidism (22). They suggested following-up thyroid functions earlier than 30 days. Mathai et al. monitored thyroid functions weekly and reported 28% of their patients had supraphysiological FT₄ levels within first month of treatment (20). Their data suggests close monitoring during the early follow-up may decrease risk of overtreatment. The mean time from initial treatment to first control visit was 14.8± 6 days in our study, and 23 (44.2%) of the infants experienced iatrogenic hyperthyroidism due to overtreatment in the first visit.

Lower doses titrated to initial hormone levels were preferred in the current study, rather than the high-doses recommended in the guidelines, still some patients experienced hyperthyroidism, thus these results suggest consideration of closer follow-up especially in patients with higher initial doses.

Study Limitations

The current study has some constraints, such as retrospective nature and small number of cases. Also, the doses as well as the follow-up schedule were not predetermined, rather they are decided by the primary endocrinologists, and time to target hormones depended on the follow-up schedule. A limited number of babies and mothers had urinary spot urinary iodine measurements. Furthermore, anthropometric parameters and data regarding long-term neuropsychological outcome are not available.

Conclusion

Our data in light of other growing number of studies suggests that standard high dose initial therapy needs to be reconsidered in CH. This may be especially true for areas where mild transient CH is endemic due to iodine deficiency. We suggest that basal serum FT₄ level may guide the initial dose of thyroxine replacement in neonates with CH, and closer follow-up should be employed for dose adjustment in the first weeks, in order to prevent overtreatment. Long-term studies are necessary to determine the validity of such treatment, and whether it has any impact on the neurocognitive outcomes of children with CH.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee

Informed Consent: Due to the retrospective nature of the study, patient consent was waived.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ceren Günbey, Alev Özön, E. Nazlı Gönc, Ayfer Alikasıfoğlu, Nurgün Kandemir. **Concept:** Ceren Günbey, Alev Özön, **Data Collection or Processing:** Ceren Günbey, Alev Özön, **Analysis or Interpretation:** Ceren Günbey, Alev Özön, E. Nazlı Gönc, Ayfer Alikasıfoğlu, Sevılay Karahan, Nurgün Kandemir. **Literature Search:** Ceren Günbey, Alev Özön. **Writing:** Ceren Günbey.

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Table 1. Pretreatment serum FT₄ and TSH levels, initial Na-LT₄ doses and days to achieve targeted serum FT₄ and TSH levels in permanent and transient congenital hypothyroidism groups.

		Initial levels			Time to achieve target hormone levels (days)	
		FT ₄ *	TSH*	Dose*	FT ₄ **	TSH**
Etiology	N	(ng/dL)	(mIU/L)	(µg/kg/day)	> 1.32 ng/dL	< 10 mIU/L
Permanent	24	0.4±0.29	95.1±51.7	9.8±2.8	15.5	18.5
Transient	28	1.05±0.4	49.6±35.1	7.1±2.9	16	16
p		<0.001	<0.001	0.003	0.927	0.079

*mean ± SS **median

Table 2. Pretreatment serum FT₄ and TSH levels, initial Na-LT₄ doses and days to achieve targeted serum FT₄ and TSH levels in high and low-dose groups.

		Initial levels			Time to achieve target hormone levels (days)	
		FT ₄ *	TSH*	Dose*	FT ₄ **	TSH**
Dose	N	(ng/dL)	(mIU/L)	(µg/kg/day)	> 1.32 ng/dL	< 10 mIU/L
High	18	0.44±0.27	102.1±54.7	11.8±1.4	12.5	17
Low	34	0.94±0.49	53.9±36.2	6.4±2.1	16	17
p		0.001	<0.001	<0.001	0.081	0.664

*mean ± SS **median