Assessment of Effective Dose of Levothyroxine in Treatment of Congenital Hypothyroid Babies: A Pilot Study

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ABSTRACT

Introduction: Congenital hypothyroidism (CH) is when newborns and infants have a low-functioning thyroid gland, leading to insufficient thyroid hormone production. Although affected babies may look normal at first, they can start to show symptoms within weeks or months after birth. The main treatment for congenital hypothyroidism is hormone replacement therapy, usually with levothyroxine (LT4). The American Academy of Pediatrics (AAP) and the European Society for Pediatrics Endocrinology (ESPE) recommend starting with a dose of 10 to 15 mcg/kg/day of levothyroxine. However, some studies suggest that using lower doses might still be effective while lowering the chance of an overdose on thyroxine.

Objective: The aim of this study was to evaluate the optimal dose of levothyroxine in the treatment of congenital hypothyroidism in Bangladeshi infants.

Materials and Methods: This study took place at the National Institute of Nuclear Medicine & Allied Sciences (NINMAS) from September 2022 to February 2024. A total of 29 newborns with diagnosed congenital hypothyroidism were enrolled. The infants received levothyroxine, prescribed mostly by physicians of Thyroid Division of NINMAS, though few of them were initially treated by outside physicians. Their thyroid hormone levels were regularly monitored with serum thyroid-stimulating hormone (TSH) test. The starting dose of levothyroxine and how long it took for the infants to reach a normal thyroid state were recorded.

Results: Among 29 subjects, male to female ratio was 15:14. It was observed that 14% of the infants started with a dose of levothyroxine less than 6 mcg/kg/day, 31% received 6-7.9 mcg/kg/day, 27% got 8-9.9 mcg/kg/day, and 28% were given 10-14 mcg/kg/day. Infants who received lower initial doses (less than 10 mcg/kg/day) reached a normal thyroid state more quickly than those who started with higher doses (10-14 mcg/kg/day). Importantly, 21 out of the 29 infants received lower doses than the usual starting amount but still showed normal thyroid function without signs of overtreatment.

Conclusion: Proper treatment of congenital hypothyroid babies is essential for appropriate growth and neurodevelopment. This study provided an important observation regarding effective dose of levothyroxine that will be helpful for adequate treatment planning of Bangladeshi congenital hypothyroid babies.

Keywords: Congenital hypothyroidism, Thyroid hormone, Levothyroxine, Newborn screening program.

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INTRODUCTION

Congenital hypothyroidism (CH), an endocrine condition, can result in severe developmental and intellectual disabilities if left untreated. It mostly impacts the skeletal and central nervous systems (CNS) and is a preventable cause of mental retardation. Reduced thyroid hormone (TH) production or action, or issues with thyroid hormone (TH) transport or metabolism during fetal development, are the causes of CH. Because there is little thyroid hormone transfer from the mother to the fetus, the illness is usually undetected at birth and, if not identified early, can cause symptoms to develop later in life (1, 2).

Before the introduction of newborn screening (NBS), CH was identified based on clinical signs; however, because many cases were not noticeable at delivery, therapy was delayed (3). By preventing severe cognitive and development problems, the NBS program has transformed the early detection and treatment of CH. It has been demonstrated that early levothyroxine (L-T4) drugs after NBS dramatically lower the risk of development delays, psychomotor dysfunction, and intellectual impairments (2). Numerous lives have been saved and permanent disabilities have been avoided thanks to this public health effort (4).

The ideal starting dose of levothyroxine to avoid developmental delays while lowering the danger of overtreatment is still up for dispute. An initial dose of 10 to 15 mcg/kg/day is advised by the European Society for Paediatric Endocrinology (ESPE) and the American

Academy of Pediatrics (AAP) (2,5). Some studies claim that lesser dosages may produce similar outcomes with fewer dangers, such as the risk of overtreatment and associated consequences (6,7). Additionally, research indicates that excessive treatment may result in long-term problems, including behavioral and developmental abnormalities, attention deficit hyperactivity disorder (6,8), and possible effects on IQ during puberty (9).

The dosage needed for effective treatment may also be influenced by differences in body composition, such as the decreased fat-free mass of South Asian newborns in comparison with white European infants (10). Studies indicate that obesity may affect the volume distribution of thyroid hormones, which could affect the amount of medication needed (11). Furthermore, the effect of levothyroxine depends on lean body mass (12). It may be assumed that lean body mass of infants of developing country and developed country is not same, therefore, Bangladeshi infants may need lower dose of levothyroxine than American infants.

Despite these concerns, there aren't any well-recognized standards for modifying levothyroxine dosage in response to treatment modifications or the severity of CH. The aim of this study was to evaluate the optimal dose of levothyroxine in the treatment of congenital hypothyroidism in Bangladeshi infants.

PATIENTS AND METHOD

From September 2022 to February 2024, this longitudinal observational study was carried out at NINMAS, Dhaka after obtaining approval from the Scientific Review Committee (SRC) and Medical Research Ethics Committee (MREC) of NINMAS. Written informed consents were obtained from parents of babies or guardians.

All diagnosed cases of congenital hypothyroidism were considered for inclusion. Babies with severe medical illnesses or other congenital diseases, such as autism, were excluded from the study. Sex, birth weight, and the amount of administered levothyroxine were the independent variables under investigation; the hypothyroid condition of the newborns was the dependent variable. Although 29 subject participated in the study, the minimum sample size was determined to be 139. Participants were chosen through purposive sampling. Shortly after birth, TSH level was tested after a thorough history and physical examination. Neonates with congenital hypothyroidism received levothyroxine treatment at NINMAS or other facilities, and their TSH levels were routinely checked. Based on the TSH levels, the levothyroxine dosage was either maintained, raised, or lowered at each follow-up. The effective dose for each participant was the one that achieved euthyroid status, with both the prior and current levothyroxine doses and serum TSH levels recorded.

Statistical analysis was carried out by using the Statistical Package for Social Sciences (SPSS) version 23.0 for Windows. A descriptive analysis was performed for all data. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies. Chi-square test was used to analyze the categorical variables and assess relationships between L-thyroxine dose. Changes in TSH levels were shown with cross tabulation. The results were presented in tables and figures. P values <0.05 was considered as statistically significant.

RESULTS

Among 29 infants with diagnosed congenital hypothyroidism, 51.7% were male and 48.3% female, with an average birth weight of 3.02 kg. None of the infants were classified as low birth weight. The starting doses of levothyroxine varied, with 14% receiving <6 mcg/kg/day, 31% receiving 6-7.9 mcg/kg/day, 27% receiving 8-9.9 mcg/kg/day, and 28% receiving 10-14 mcg/kg/day. A significant association was found between starting dose and euthyroidism attainment, with higher doses linked to higher rates of hyperthyroidism. Study findings are summarized in tables and figures.

Table 1: Demographic characteristic of the diagnosed congenital hypothyroid babies

Sex	Number	Percentage
Male	15	51.7
Female	14	48.3
Total	29	100.0
Birth weight (Mean ±SD)	3.02 (±0.42)	Range 2.50-4.00

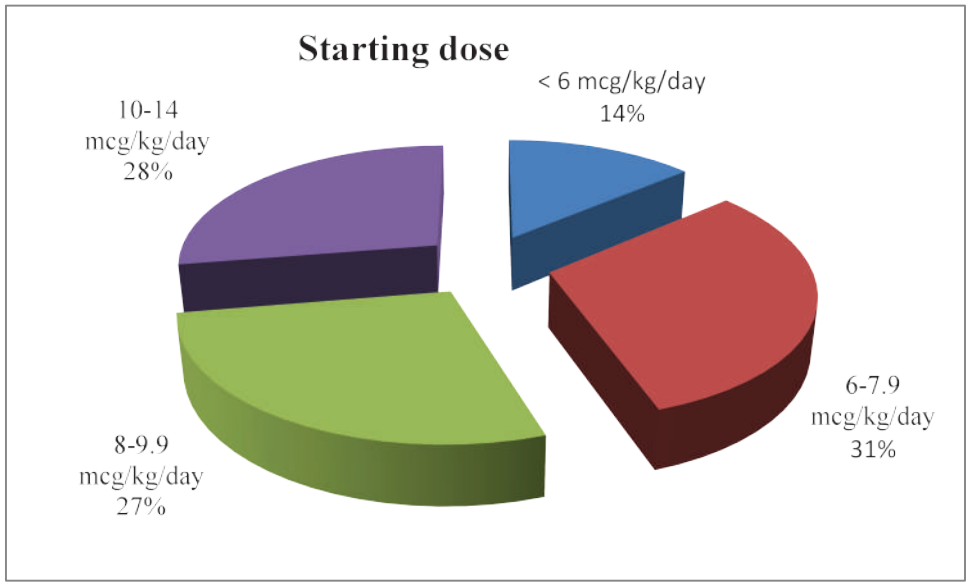

Figure 1: Different starting doses of levothyroxine (n=29)

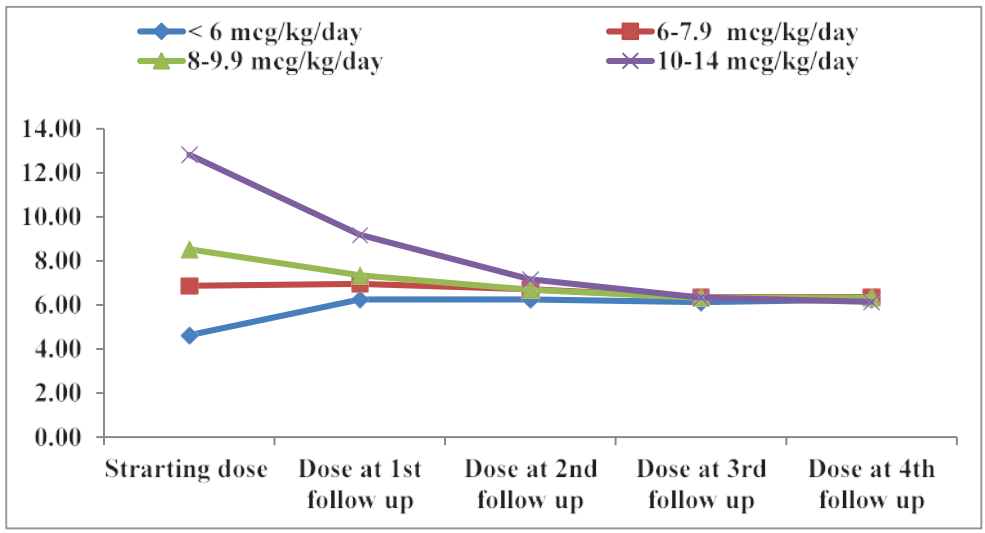

Figure 2: Line chart showing dose adjustment of congenital hypothyroid babies with different starting dose of levothyroxine after each follow up according to their TSH report (n=29)

Table 2: Thyroid status of congenital hypothyroid babies at 1st follow up according to different starting dose of levothyroxine (n=29)

Thyroid status at 1st follow up after 2 months	Starting dose of levothyroxine after birth				*P* value
	< 6 mcg/kg/day n=4	6-7.9 mcg/kg/day n=9	8-9.9 mcg/kg/day n=8	10-14 mcg/kg/day n=8	
Hyperthyroid	0	2 (22.2%)	7 (87.5%)	8 (100%)	
Euthyroid	0	6 (66.7%)	1 (12.5%)	0	<0.001
Hypothyroid	4 (100%)	1 (11.1%)	0	0	

Table 3: Thyroid status of congenital hypothyroid babies with different starting dose of levothyroxine at 2nd follow up after dose adjustment according to their TSH report (n=29)

Thyroid status at 2nd follow up after 6 months	Starting dose of levothyroxine after birth				*P* value
	< 6 mcg/kg/day n=4	6-7.9 mcg/kg/day n=9	8-9.9 mcg/kg/day n=8	10-14 mcg/kg/day n=8	
Hyperthyroid	1 (25.0%)	0	1 (14.3%)	7 (85.7%)	
Euthyroid	2(50.0%)	9 (100%)	7 (85.7%)	1 (14.3%)	<0.001
Hypothyroid	1(25.0%)	0	0	0	

Table 4: Thyroid status of congenital hypothyroid babies with different starting dose of levothyroxine at 3rd follow up after dose adjustment according to their TSH report (n=29)

Thyroid status at 3rd follow up after 1 year	Starting dose of levothyroxine after birth			
	< 6 mcg/kg/day n=4	6-7.9 mcg/kg/day n=9	8-9.9 mcg/kg/day n=8	10-14 mcg/kg/day n=8
Hyperthyroid	0	0	0	2 (25.0%)
Euthyroid	4 (100%)	9 (100%)	8 (100%)	6 (75.0%)
Hypothyroid	0	0	0	0

Table 5: Thyroid status of congenital hypothyroid babies with different starting dose of levothyroxine at 4th follow up after dose adjustment according to their TSH report (n=29)

Thyroid status at 4th follow up after 1.5 year	Starting dose of levothyroxine after birth			
	< 6 mcg/kg/day n=4	6-7.9 mcg/kg/day n=9	8-9.9 mcg/kg/day n=8	10-14 mcg/kg/day n=8
Hyperthyroid	0	0	0	0
Euthyroid	4 (100%)	9 (100%)	8 (100%)	8 (100%)
Hypothyroid	0	0	0	0

Table 6: Thyroid status of congenital hypothyroid babies with different starting dose of levothyroxine at all four follow ups after dose adjustment according to their TSH report (n=29)

Dose of steroid	Thyroid status	1st follow up (after 2 months)	2nd follow up (after 6 months)	3rd follow up (after 1 year)	4th follow up (after 1.5 year)
< 6 mcg/kg/day	Hyperthyroid	0	1 (25.0%)	0	0
	Euthyroid	0	2(50.0%)	4 (100%)	4 (100%)
	Hypothyroid	4 (100%)	1(25.0%)	0	0
6-7.9 mcg/kg/day	Hyperthyroid	2 (22.2%)	0	0	0
	Euthyroid	6 (66.7%)	9 (100%)	9 (100%)	9 (100%)
	Hypothyroid	1 (11.1%)	0	0	0
8-9.9 mcg/kg/day	Hyperthyroid	7 (87.5%)	1 (14.3%)	0	0
	Euthyroid	1 (12.5%)	7 (85.7%)	8 (100%)	8 (100%)
	Hypothyroid	0	0	0	0
10-14 mcg/kg/day	Hyperthyroid	8 (100%)	7 (85.7%)	2 (25.0%)	0
	Euthyroid	0	1 (14.3%)	6 (75.0%)	8 (100%)
	Hypothyroid	0	0	0	0

Table (2-6) shows that the most effective starting dose of levothyroxine was 6-7.9 mcg/kg/day. Infants receiving this dose achieved euthyroid status by the second follow-up. Higher doses (10-14 mcg/kg/day) led to hyperthyroidism, while lower doses (<6 mcg/kg/day) caused persistent hypothyroidism. Euthyroid status was achieved across all doses by the fourth follow-up.

DISCUSSION

In this study, there was a male preponderance among the subjects (Table 1). Azim et al. (2022) reported that in case of congenital hypothyroidism, the number of affected females was almost 1.5 times higher than males, with a distribution of 41.9% male and 58.1% female. On the other hand, Esposito et al. (2022) reported a Female/Male distribution of 61.8% and 38.2%, respectively (13, 14). The higher number of male infants in the present study could be attributed to socio-economic and cultural factors influencing healthcare accessibility. It is possible that a preference for boys over girls led to inequity in healthcare, resulting in more male infants receiving attention and treatment.

The mean birth weight of the study participants was 3.02 ± 0.42 kg (Table 1), and none of the infants were classified as having low birth weight. The starting doses of levothyroxine in our study varied, with 14% receiving <6 mcg/kg/day, 31% receiving 6-7.9 mcg/kg/day, 27% receiving 8-9.9 mcg/kg/day, and 28% receiving 10-14 mcg/kg/day (Figure-1).

In an Asian study by He et al. (2022), patients were divided into four groups based on their initial TSH levels. Group A (TSH ≥100 mIU/L) received a dose of 10 mcg/kg/day, while Group B (TSH 20-100 mIU/L) received 5-8 mcg/kg/day, and Groups C and D (TSH between 4.6 mIU/L and 20 mIU/L) were prescribed 3-4 mcg/kg/day. The study showed that despite initial dosing based on TSH levels, a portion of patients in these groups required dose modifications after one month to normalize thyroid function (15). This aligns with the current study's observation that levothyroxine dosage often requires adjustment based on thyroid function.

In the present study, at the first follow-up (Table 2), among 29 infants, those receiving <6 mcg/kg/day had doses increased to 6-7.9 mcg/kg/day due to hypothyroidism. Nine infants on 6-7.9 mcg/kg/day had mixed outcomes, while seven on 8-9.9 mcg/kg/day and all on 10-14 mcg/kg/day developed hyperthyroidism and had doses reduced.

At the second follow-up (Table 3), the <6 mcg/kg/day group had varied outcomes, with one hyperthyroid, two euthyroid, and one hypothyroid. All infants on 6-7.9 mcg/kg/day achieved euthyroid status, seven on 8-9.9 mcg/kg/day became euthyroid, and all on 10-14 mcg/kg/day achieved euthyroid status.

By the third follow-up (Table 4), all the infants who received initial doses of <6 mcg/kg/day, 6-7.9 mcg/kg/day, and 8-9.9 mcg/kg/day achieved euthyroid status, and this continued into the fourth follow-up (Table 5), where all 29 infants achieved euthyroid status. Although the recommended dose is 10-15 mcg/kg/day, our study's highest dose was 10-14 mcg/kg/day due to the small sample size.

In a study by Esposito et al. (2022), initial doses of L-T4 between 10-12.5 mcg/kg/day and 12.6-15 mcg/kg/day were associated with normal growth and neurodevelopmental outcomes (14). However, our study found that higher doses led to hyperthyroidism, differing from their findings. Clinical guidelines recommend an initial dose of 10-15 mcg/kg/day for congenital hypothyroidism, aiming to achieve normal serum FT4 and TSH levels (2,5). Studies by Bauer and Wassner (2019) and Cherella and Wassner (2020) supported this (16,17) observation.

However, some studies suggest that lower dosages can achieve the same goals while minimizing the risk of overdose (6). Schömig et al. (2018) showed that a dose of 6.3 mcg/kg/day achieved euthyroidism at four months of age, with a dose increase to 7 mcg/kg/day later maintaining control (18). Similarly, Craven and Frank (2018) reported that most patients with initial doses of >12.5 mcg/kg/day required dose reductions, emphasizing the importance of dose adjustments (19).

This study supports the findings that excessive levothyroxine dosing can lead to hyperthyroidism and that a more moderate approach with doses of 6-7.9 mcg/kg/day is effective and results in a balanced thyroid state without significant risks of overtreatment or hypothyroidism. Limitations of the study include the small sample size, which may affect the generalizability of the results.

CONCLUSION

The present study explored the initial levothyroxine dosage for neonates with congenital hypothyroidism and the time needed to normalize thyroid function. It was observed that high initial doses often led to hyperthyroidism before improvement, posing potential risks. However, starting with a lower dosage yielded more favorable outcomes, as infants achieved healthy thyroid function more quickly and without the risk of hyperthyroidism. This approach highlights the benefit of cautious dosing for safer and more effective treatment.

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