International Journal of Contemporary Pediatrics
Radhakrishnan R et al. Int J Contemp Pediatr. 2017 Nov;4(6):1969-1974
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20174155

Original Research Article

Effectiveness of bedtime levothyroxine intake as compared to morning levothyroxine intake in children

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Received: 29 August 2017
Accepted: 02 September 2017

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ABSTRACT

Background: The study was conducted to assess the effectiveness of bedtime Levothyroxine administration as compared to morning Levothyroxine administration in thyroid profile, renal and lipid parameters, anthropometric and vital parameters in children attending endocrinology OPD at a tertiary care center in Southern India.
Methods: It is an open label randomized control study. 154 children who were diagnosed to have hypothyroidism, on levothyroxine supplementation and in euthyroid state at the start of study were included. Children were randomly allocated into two groups. One group received levothyroxine in early morning (1hr before food) and another group received levothyroxine in bedtime (2hrs after food) up to 3 months. At baseline, 6 weeks and 12weeks, thyroid profile, renal and lipid parameters and vital parameters were measured during follow up. Anthropometric parameters were measured at baseline and 12 weeks.
Results: In 6th week analysis, mean TSH level of morning group (2.35±0.38 mIU/L) and bedtime group (2.42±0.40 mIU/L) did not show any statistical difference (p=0.8). In 12th week analysis mean TSH level of morning group (2.18±0.34 mIU/L) and bedtime group (1.90±0.33 mIU/L) did not show any statistical difference (p=0.24). At 6th week analysis, mean free T4 level of bedtime group (1.45±0.08 ng/dl) is higher than morning group (1.33±0.2 ng/dl). This difference is statistically significant (p= 0.03). At 12 th week analysis, mean free T4 level of bedtime group (1.65±0.04 ng/dl) is higher than morning group (1.31±0.06 ng/dl). This difference is statistically significant (p<0.00001). A 12weeks, the difference in mean serum cholesterol of morning group (152.79±4.59 mg/dl) and bedtime group (143.58±3.059 mg/dl) is statistically significant (p=0.001). At 6 and12 weeks, other parameters like serum triglycerides, HDL cholesterol, renal parameters, anthropometry, vital parameters of morning group and bedtime group did not show any statistical significant difference.
Conclusions: There is a significant improvement in free T4 level when levothyroxine was taken at bedtime. The efficacy of bedtime regimen of levothyroxine is quite comparable to the efficacy of morning regimen. There is considerable decrease in serum cholesterol level when levothyroxine was taken at bedtime. Bedtime regimen may result in good compliance in school going children. Parents should be allowed to choose either morning or bedtime regimen depending on their convenience.

Keywords: Bedtime group, Free T4, Levothyroxine, Morning group, TSH

INTRODUCTION

Decreased thyroid hormone has significant impact on growth and development. Untreated congenital hypothyroidism leads to devastating intellectual and developmental consequences. Acquired hypothyroidism affects growth and school performance. Levo-thyroxine is used in treatment of both congenital and acquired

hypothyroidism. Levo-thyroxine commonly used because of its stability, content uniformity, low cost, lack of allergenic foreign proteins and long half life which allow once daily administration.

For treatment of hypothyroidism, levothyroxine is supplemented in early morning in empty stomach 30 to 60 minutes before breakfast because food intake interferes with levothyroxine absorption.[1,2] Adherence to the timing of levothyroxine administration before breakfast is cumbersome in children, especially who are school going. The refusal of children and forgetfulness of parents are quite common, when parents are busy preparing the children for school. If it is proved that evening dose of levothyroxine is equally efficacious as morning dose in children, it will be useful for parents of hypothyroid children.

In previous pilot study changing of Levo-thyroxine regimen from morning to evening time has improved the TSH level.[3,4] We performed this study to assess the effectiveness of bedtime levothyroxine administration as compared to morning levothyroxine administration.

METHODS

Open label randomized control study conducted at endocrinology OPD of Institute of Child Health and Hospital for Children during the period between September 2015 to August 2016. Children above 3 years of age on follow up in endocrinology OPD who were diagnosed to have hypothyroidism, on levothyroxine supplementation and in euthyroid state at the start of study after meeting inclusion and exclusion criteria. For calculation of sample size, results from the pilot study conducted by Bolk et al was used. To get a significant difference in TSH of 1.5 mIU/L with a power of 80% 77 subjects were enrolled in each group. Children with GIT disorder, malabsorption syndrome or taking medication known to interfere with uptake of levothyroxine were excluded from the study.[3-5]

Ethical clearance was obtained from the Institutional Review Board. Informed written consent was obtained from the parents of the study subjects. Strict confidentiality of data was maintained throughout the study.

Out of 250 children who were on regular follow up, 154 children satisfying inclusion and exclusion criteria were recruited into the study. Informed written consent was obtained. Children were randomly allocated into two groups. One group received levothyroxine at early morning (1hr before food) and another group received levothyroxine at bedtime (2hrs after food) upto 3 months.

Before the start of the study dose of levothyroxine was adjusted to achieve the euthyroid state but after starting the study, same dose of levothyroxine was maintained throughout. The baseline demographic characteristics and clinical characteristics were obtained from all the children at the start of study. Age was calculated in months from the date of birth.

Anthropometric parameters were measured at baseline and 12 weeks. Vital parameters, TSH, free T4, lipid profile and renal parameters were measured at baseline, 6 weeks and 12 weeks. Z-score was calculated for systolic and diastolic BP measurements separately. Anthropometric parameters were also transformed into Z scores based on the age of the child.

Thyroid function test was performed on early morning venous blood sample after 12 hours of fasting. TSH and free T4 levels were measured using enzyme immunoassay method.[6] Early morning fasting venous blood sample was collected for lipid profile analysis. Serum concentrations of Total cholesterol (CHOD POD method), HDL (direct assay method), Triglycerides (GPO method) were measured. Renal parameters like blood urea (enzymatic GLDH method) and serum creatinine (kinetic Joffe's method) were measured.

All the descriptive statistics, frequency histograms and bar charts were created using Gnumeric spreadsheet (version: 1.12.28), a light weight spread sheet developed by Gnome open source project. All parametric and non parametric tests and tests for categorical data were done in R programming language (R version 3.2.3 (2015-12-10)– "Wooden Christmas-Tree" Copyright © 2015 The R Foundation for statistical computing). The computing platform was x86_64-Arch-Linux-gnu (64-bit).

RESULTS

At baseline (0 weeks), all primary and secondary parameters were comparable between morning and bedtime group.

Table 1: Baseline parameters of morning and bedtime group.

Parameter	Morning	Bedtime	p value
TSH	2.17±0.36	1.93 ± 0.34	0.32
Free T4	1.39±0.66	1.40±0.09	0.79
Urea	23.79±0.87	23.70±0.94	0.88
Creatinine	0.60±0.02	0.59±0.02	0.51
Cholestrol	151.57±5.86	152.13±4.14	0.88
Triglyceride	54.29±2.02	53.47±2.16	0.58
HDL	50.90±2.12	51.79±0.20	0.54
Height	-0.30±0.13	-0.40±0.128	0.28
Weight	0.03 ± 0.12	-0.070±0.12	0.23
BMI	0.28±0.16	0.19±0.17	0.41
Systolic BP	-0.02±0.19	-0.03±0.17	0.91
Diastolic BP	-0.05±0.18	-0.04±0.18	0.92

At sixth week, mean free T4 levels of bedtime group (1.45ng/dl) was higher than morning group (1.33ng/dl). The difference in sixth week mean free T4 levels of two groups (-0.12ng/dl) was statistically significant (p=0.03).

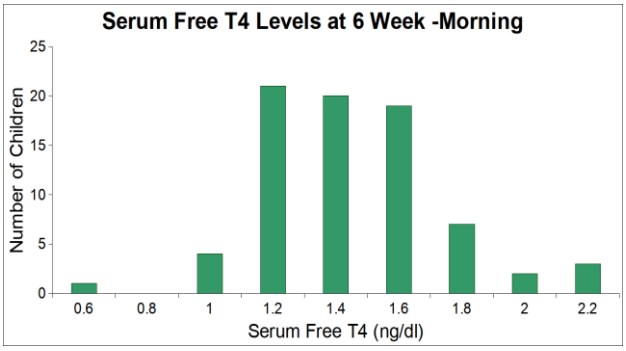

Figure 1: Morning free T4 levels at 6 weeks.

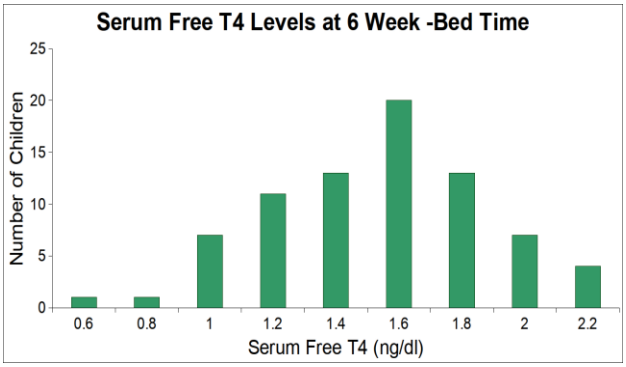

Figure 2: Bed time free T4 levels at 6 weeks.

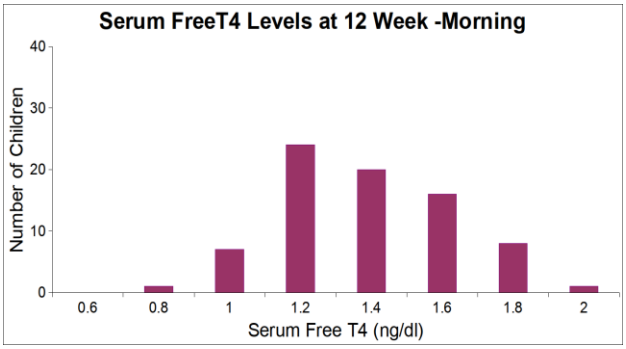

Figure 3: Morning serum free T4 levels at 12 weeks.

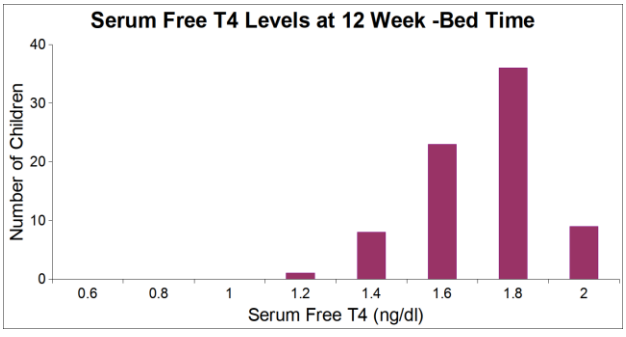

Figure 4: Bed time serum free T4 levels at 12 weeks.

At twelfth week, mean Free T4 group (1.65ng/dl) is higher than morning group (1.31ng/dl). The difference in twelfth week mean Free T4 levels of two groups (-0.34ng/dl) is statistically significant (p<0.00001).

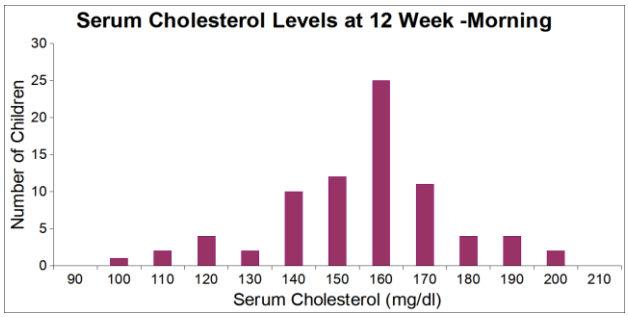

Figure 5: Morning serum cholesterol levels at 12 weeks.

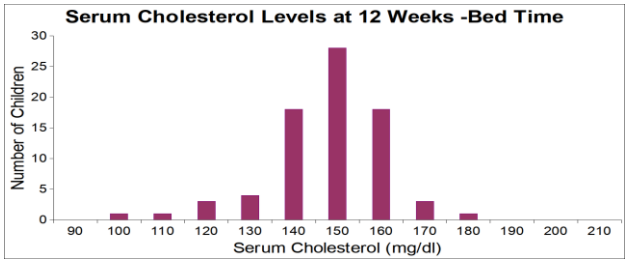

Figure 6: Bed time serum cholesterol levels at 12 weeks.

The twelfth week mean serum cholesterol level of morning group (152.79mg/dl) is higher than bedtime group (143.58mg/dl). The difference in twelfth week mean serum cholesterol level of two group (9.21mg/dl) is statistically significant (p=0.001).

Table 2: 12th week parameters of morning and bedtime group.

Parameter	Morning	Bedtime	p value
TSH	2.18±0.34	1.90±0.33	0.24
Free T4	1.31±0.06	1.65±0.04	<0.00001
Urea	23.36±0.88	23.54±0.94	0.78
Creatinine	0.597±0.02	0.596±0.02	0.093
Cholesterol	152.79±4.59	143.58±3.059	0.001
Triglyceride	53.78±2.21	53.17±2.12	0.69
HDL	52.29±2.04	51.47±2.15	0.58
Height	-0.32±0.13	-0.437±0.13	0.25
Weight	-0.02±0.12	-0.12±0.12	0.25
BMI	0.22±0.16	0.15±0.18	0.54
Systolic BP	-0.024±0.18	-0.015±0.16	0.94
Diastolic BP	-0.15±0.18	0.02±0.16	0.16

DISCUSSION

There are many studies done in adults to assess the effectiveness of morning levothyroxine administration versus bedtime levothyroxine administration with mixed results.

To the best of our knowledge, this is the first pediatric study done till date to evaluate the effectiveness of bedtime levothyroxine as compared to morning levothyroxine administration.

In present study mean age of children in morning group is 8.32 years and in bedtime group is 8.44 years. There is no statistically significant difference in mean age of two groups (p=0.8). Sex distribution ratio of male: female in morning group is 0.51:1 and in bedtime group is 0.48:1. The difference in sex distribution among these two groups is not statistically significant (p=1).

Between the morning and bedtime group, the baseline level of TSH, free T4, blood urea, Serum creatinine, cholesterol, triglycerides, HDL cholesterol and Z scores of height, weight, BMI, systolic BP and diastolic BP do not show any statistical significant difference.

Comparison of TSH levels

In 6th week analysis, mean TSH level of morning group (2.35±0.38 mIU/L) and bedtime group (2.42±0.40 mIU/L) did not show any statistical difference (p=0.8). In 12th week analysis mean TSH level of morning group (2.18±0.34 mIU/L) and bedtime group (1.90±0.33 mIU/L) did not show any statistical difference (p=0.24). This finding is consistent with the study done by Bolk N et al, Rajput R et al and Elliot DP but is in contrast to the study done by Bach-Huynh TG et al.[1,3,4,7,8]

Bolk N et alconducted a randomised double blind cross over trial in 105 adult patients with primary hypothyroidism over a period of 6 months with switch over from morning to bedtime and viceversa at 3 months.[1] The difference in TSH (at 12wks and 24wks) between morning (-0.92 mIU/L) and bedtime group (1.57 mIU/L) is statistically significant (p<0.001). Rajput R et al conducted a clinical study.[4] 152 newly diagnosed primary hypothyroid adults were chosen and divided into two groups (group 1 given levothyroxine in morning and group 2 at bedtime).

Mean serum TSH levels between morning (5.13±9.36 mIU/L) and bedtime group (3.27±4.19 mIU/L) done at the end of 12wks did not show any statistical significant difference (p=0.31). Elliot DP conducted a retrospective chart review in 2001. 15 elderly hypothyroid patients were chosen. The decrease in mean serum TSH level (0.286±1.722mIU/L) when levothyroxine supplementation was changed from morning to midnight did not show any statistical significance (p=0.532).[8]

Bach-Huynh TG et al conducted a randomised cross over study.[3] 65 adult study subjects were chosen and randomised into three 8 week regimens (fasting, bedtime, with breakfast) in a three period crossover design. Mean serum TSH levels was significantly high in bedtime group (2.19 mIU/L) when compared to before breakfast group (1.06 mIU/L) (p<0.001).

At 6 weeks, 2 children in morning group and 3 children in bed time group had marginal rise in their TSH levels. These values became normal at 12 weeks.

Comparison of free T4

At 6th week analysis, mean free T4 level of bedtime group (1.45±0.08 ng/dl) is higher than morning group (1.33±0.2 ng/dl). This difference is statistically significant (p= 0.03). At 12th week analysis, mean free T4 level of bedtime group (1.65±0.04 ng/dl) is higher than morning group (1.31±0.06 ng/dl). This difference is statistically significant (p<0.00001). These findings are consistent with the study done by Bolk N et al[1], Rajput R et al but contradictory to the study done by Bach-Huynh TG et al.[1,3,4]

In Bolk N et al study, the difference in free T4 (at 12wks and 24wks) between morning (0.11 ng/dl) and bedtime group (-0.04 ng/dl) is statistically significant (p=0.01).[1] In Rajput R et alstudy, mean serum free T4 levels between morning (1.5±0.33 ng/dl) and bedtime group (1.48±0.31 ng/dl) done at the end of 12wks did not show any statistical significant difference (p=0.31).[4] In Bach-Hyunh TG et al study, free T4 value was less in bedtime group (1.34 ng/dl) when compared to morning group (1.35 ng/dl) but this difference is not statistically significant (p=0.72).[3]

In present study, the increase in mean free T4 value in bedtime group may be due to the better bioavailability of levothyroxine in bedtime (2 hours after dinner), decreased gastrointestinal movement during night time, more gastric acidity (circadian rhythm) in night and no food or drug intake after levothyroxine intake.[1,4,9] In morning children usually wakeup very late and there is very less time gap between levothyroxine intake and breakfast. So, there is less bioavailability of levothyroxine compared to bedtime group. Also snacks or other drug intake interferes with levothyroxine absorption.[10-16] In hypothyroid children on levothyroxine, free T4 increases without any change of TSH.

Comparison of renal parameters

At 6th week, mean blood urea level of morning group (24.14±0.82 mg/dl) and bedtime group (23.79±0.86 mg/dl) did not show any statistical significant difference (p=0.56). At 12th week, mean blood urea level of morning group (23.36±0.88 mg/dl) and bedtime group (23.54±0.94 mg/dl) did not show any statistical significant difference (p=0.78).

At 6th week, mean serum creatinine level of morning group (0.6±0.02 mg/dl) and bedtime group (0.59±0.02 mg/dl) did not show any statistical significant difference (p=0.57). At 12th week, mean serum creatinine level of morning group (0.597±0.02 mg/dl) and bedtime group (0.596±0.02 mg/dl) did not show any statistical significant difference (p=0.93). This finding is consistent

with the study done by Bolk N et al in which the difference in serum creatinine level (at 12wks and 24wks) between morning (-0.03 mg/dl) and bedtime group (0.00 mg/dl) did not show any statistically significant difference (p=0.13).[1] The possible explanation may be that, alteration in renal function occurs only in chronic uncontrolled hypothyroid subjects but in our study all children were in euthyroid state at the start of study and throughout the study.[9,17]

Comparison of lipid profile

At 6 weeks, mean serum cholesterol, triglycerides, HDL cholesterol of morning group (151.17±5.6mg/dl, 53.88±1.92mg/dl, 53.95±1.98mg/dl) and bedtime group (147.71±5.82mg/dl, 54±2.56mg/dl, 53.57±1.8mg/dl) did not show any statistical significant difference.

A 12 week, the difference in mean serum cholesterol of morning group (152.79±4.59 mg/dl) and bedtime group (143.58±3.059 mg/dl) is statistically significant (p=0.001). This may due to the better bioavailability of levothyroxine at bedtime that stimulates the expression of hepatic LDL receptor and metabolism of cholesterol to bile acids that lead to decrease in mean cholesterol level in bedtime.[1,18,19] This finding is contradictory to the study done by Rajput R et al in which there was no significant difference in serum cholesterol levels between morning and bedtime group.[4] Also in the study done by Bolk N et al, there was no significant difference in serum cholesterol levels between morning and bedtime group (p=0.22).[1]

At 12 weeks, mean serum triglycerides and HDL cholesterol of morning group (53.78±2.21 mg/dl, 52.29±2.04 mg/dl) and bedtime group (53.17±2.12 mg/dl, 51.47±2.15 mg/dl) did not show any statistical significant difference (p=0.69, p=0.58). This is similar to the study done by Rajput R et al in which there was no significant difference in serum triglyceride and HDL levels between morning and bedtime group.[4]

Comparison of anthropometric parameters

At 12 weeks, anthropometric indices like height, weight and BMI in Z score of morning group (-0.32±0.13, -0.02±0.12, 0.22±0.16 respectively) and bedtime group (-0.43±0.13, -0.12±0.12, 0.15±0.18 respectively) did not show any statistical significant difference (p=0.25, p=0.25, p=0.54 respectively). This finding is similar to the study done by Bolk N et al, in which there was no significant difference in BMI between morning and bedtime group (p=0.09).[1]

Comparison of vital parameters

At 6 weeks, the mean heart rate in morning group was 99.04 beats/min and in bedtime group was 98.43 beats/min. The mean Z score of Systolic BP and Diastolic BP of morning group (-0.04±.18, 0.07±0.17) and bedtime group (0.14±0.18, -0.02±0.20) did not show any statistical significant difference (p=0.18 and 0.5 respectively).

At 12 weeks, the mean heart rate in morning group was 96.84 beats/min and in bedtime group was 98.48 beats/min. In Bolk N et alstudy, there was no significant difference in heart rate between morning and bedtime group (p=0.40).[1] The mean Z score of Systolic BP, Diastolic BP of morning group (-0.024±0.18, -0.15±0.18) and bedtime group (-0.015±0.16, 0.02±0.16) did not show any statistical significant difference (p=0.94 and 0.16 respectively).

CONCLUSION

The dosage of levothyroxine which maintained euthyroid status (as reflected by TSH and fT4 level) when taken in early morning empty stomach is also likely to maintain euthyroid status when it is administered at bedtime. There is a significant improvement in free T4 level when levothyroxine was taken at bedtime. There is considerable decrease in serum cholesterol level when levothyroxine was taken at bedtime.

Effects of bedtime levothyroxine administration on anthropometry, vital parameters and other parameters in lipid profile are comparable to those observed in children taking morning levothyroxine.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Radhakrishnan R, Venkatasamy S, Pyarejan KS, Jayachandran K. Effectiveness of bedtime levothyroxine intake as compared to morning levothyroxine intake in children. Int J Contemp Pediatr 2017;4:1969-74.