

Original Research Article

The dilemma of levothyroxine replacement timing: comparison of bedtime versus early-morning replacement of levothyroxine in post total thyroidectomy patients

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ABSTRACT

Background: Following total thyroidectomy levothyroxine replacement is imperative and required lifelong. There are many studies done to assess the effectiveness of levothyroxine administration in hypothyroid patients with intact thyroid gland. This study was intended to evaluate if bedtime dose of levothyroxine is same as early-morning replacement of levothyroxine in post total thyroidectomy patients.

Methods: A randomized study was conducted on patients who underwent total thyroidectomy for benign thyroid disorders from September 2017 to August 2018 at endocrine surgery department in a tertiary care institute (South India). Patients were randomly assigned into two groups by chit method, Group A received levothyroxine early morning one hour before food and the Group B received levothyroxine at bedtime two hours after food up to 3 months. 6 weeks and 12 weeks fT4 (freeT4) and TSH (thyroid stimulating hormone) were measured during follow up.

Results: A total of 123 patients were recruited and randomized into either of the study groups. 58 patients in Group A and 53 patients in Group B were considered for statistical evaluation. At 6th and 12th week assessment mean TSH level of early-morning group and bedtime group had no statistical difference. At 6th week assessment, mean fT4 level of bedtime group was insignificantly than the early morning group. At 12th week assessment, mean fT4 level of bedtime group was higher than early-morning group, and the difference was also statistically significant ($p=0.0005$).

Conclusions: Clinicians may consider prescribing levothyroxine at bedtime as an alternative to the conventional morning dose.

Keywords: Levothyroxine, Bedtime dose, Total thyroidectomy, Euthyroidism

INTRODUCTION

Hypothyroidism is a very common endocrine disorder and levothyroxine, a commonly prescribed drug with great stability and absorption. Majority of it is absorbed in the small intestine, generally abiding by the circadian rhythm. Post total thyroidectomy levothyroxine replacement is obligatory and needed throughout life. Typically this drug is administered at least an hour prior to breakfast, nevertheless many patients find it bothersome to take this drug on an empty stomach in the

morning because of their lifestyle, customs and circumstances.^{1,2} Patients usually request their surgeon to prescribe the drug at some other time of the day. The well understood TSH circadian rhythm accounts for high TSH levels in the evening with slow tapering and low levels during the subsequent day. Likewise, a preliminary study by Bolk et al, switching levothyroxine from morning to evening time has shown improvement in the thyroid profile.^{2,3} There are many studies done to assess the advantage of bedtime levothyroxine administration in hypothyroid patients with intact thyroid gland.⁴ This

study was started with the hypothesis that evening dose of levothyroxine was equivalent to bedtime replacement of levothyroxine. Hence we studied fT_4 and TSH levels to evaluate if bedtime replacement of levothyroxine was equivalent to early-morning replacement in post total thyroidectomy patients, where the replacement dose and fT_4 and TSH estimation will not be confounded by the natural production of thyroid hormones by in situ thyroid gland.

METHODS

Study design and subjects

This was an open labelled, randomized control study intended to compare the serum fT_4 and TSH level between patients taking bedtime dose with patients in parallel groups taking early-morning dose of levothyroxine following total thyroidectomy. The study was done in accordance with the Indian version of good clinical practice guidelines, declaration of Helsinki and Ethical guidelines for Biomedical Research by the Indian Council of Medical Research. Written informed consent was obtained from each patient.

The study was conducted in Department of Endocrine surgery, Madras Medical College, Tamil Nadu, India after obtaining the institutional ethical clearance. The study included all patients who underwent total thyroidectomy for benign thyroid disorders during September 2017 to August 2018 (one year). Patients with thyroid malignancy, gastrointestinal disease, pregnancy, significant renal or cardiac disease or taking medication known to interfere with absorption of levothyroxine like iron sulphate, calcium preparations and aluminium antacids were excluded.

Study intervention, sample size, randomisation

Those satisfying the inclusion criteria, attending the outpatient clinic, compliant and willing to participate were enrolled in the study. Randomisation was done by chit method and two groups were allocated with a minimum of 60 patients each. Instructions to take medications were provided by a research nurse. Sample size was calculated to be a minimum of 75 patients with a power of 80% and difference of TSH of $1\mu\text{IU/ml}$, derived from the pilot study by Bolk et al.² Group A (early-morning) included 62 patients and Group B (bedtime) included 54 patients. 5 patients were lost to follow up. The patients received levothyroxine once daily. Patients taking early morning dose of levothyroxine were asked to take it at least an hour before breakfast, and those taking evening dose were instructed to take the same levothyroxine minimum 2 hours after dinner. Levothyroxine was supplied from the hospital pharmacy. Initial dosage was calculated as $1.6\ \mu\text{g/kg}$ body weight, and the closest commercially available dosage was started (75/100/125/150 μg).

Outcome assessment and follow up

In the setting of non-achievement of euthyroidism (defined by normalization of fT_4 and TSH) at the end of six weeks, the dose was increased by $25\mu\text{g/day}$. The patients were followed up for 12 weeks and fT_4 and TSH were repeated. The containers with tablets were checked for compliance. Any patient was allowed to withdraw from the study in case of any acute illness, non-compliance or protocol breach. Weekly phone calls were conducted to supervise and remind patients to adhere to the timings and dietary advice.

Laboratory estimation

Biomerieux mini vidas analyzer was used to assess fT_4 (normal range: 0.82-1.51 ng/dl) and TSH (normal range: 0.25-5.0 $\mu\text{IU/ml}$), tests were done with VIDAS[®] thyroid panel based on Enzyme linked fluorescent assay technique. Investigations were done in the Department of Endocrine surgery, Madras medical college. Blood samples were taken between 9AM and 10AM for all patients after overnight fasting but tablets were not withheld.

Statistical analyses

The primary end point was a change in TSH and fT_4 levels at 6 and 12 weeks after early-morning and bedtime levothyroxine intake. The collected data were analysed with IBM.SPSS statistics package software 23.0 Version. The data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean and standard deviation were used for continuous variables. The Paired sample t-test was used to find the significant difference between the bivariate samples in paired groups & the unpaired sample t-test was used for Independent groups. Chi-Square test was used similarly to find the significance in categorical data. If the expected cell frequency is less than 5 in 2×2 tables then the Fisher's Exact was used. In all the above statistical tools, the probability value 0.05 was considered significant.

RESULTS

A total of 123 patients who have undergone total thyroidectomy were enrolled the study. A total of 116 patients were eligible after subjecting to inclusion criteria. 5 patients were lost on follow up, 111 patients were considered for analyses (Figure 1). Baseline characteristics between the 2 groups were comparable. Gender distribution in our study leaned towards a female preponderance. The distribution of 3 doses of levothyroxine used in the 2 study groups were largely similar. All patients underwent total thyroidectomy with colloid goitre being the most common histopathological diagnosis. Postoperative complications included temporary hypocalcemia in 17 patients and unilateral recurrent laryngeal nerve palsy in 2 patients (Table 1).

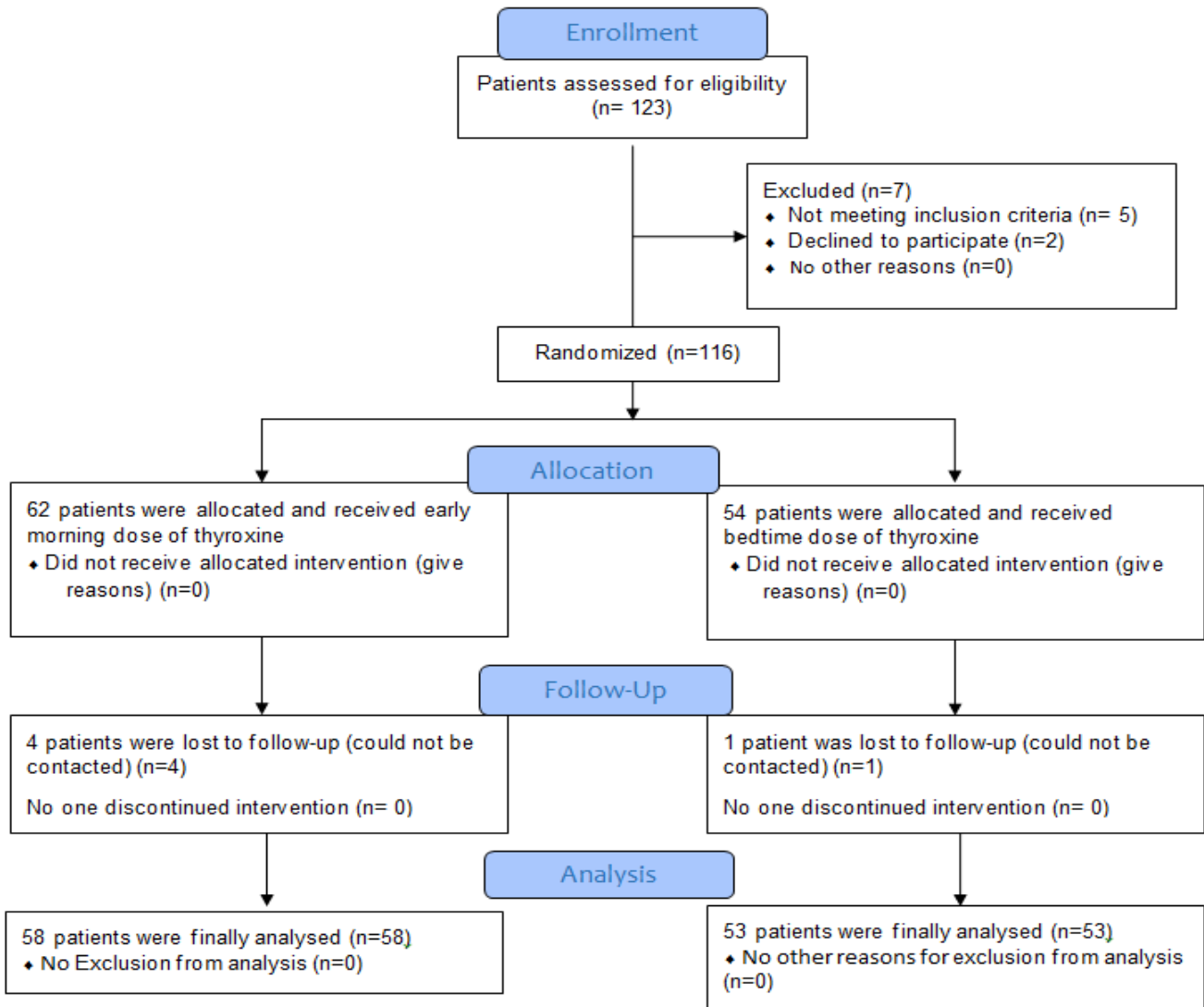


Figure 1: Study flowchart from enrollment to completion.

Table 1: Baseline characteristics of the patients.

| Characteristic | Morning dose levothyroxine (n=58) | Bedtime dose levothyroxine (n=53) | P value |
|--|-----------------------------------|-----------------------------------|---------|
| Age in years (Mean) | 41 | 42 | 0.85 |
| Female gender (%) | 93.1% | 84.9% | |
| Weight in kg (Mean) | 60.28 | 60.89 | |
| BMI(kg/m ²) | 25.36 | 24.85 | 0.28 |
| TSH (4 weeks) | 2.18±1.36 | 1.90±0.35 | 0.35 |
| ft ₄ (4 weeks) | 1.36±0.65 | 1.45±0.10 | 0.8 |
| Thyroxine dose (1.6 mcg/kg) | | | |
| 75 mcg | 13.8% | 13.2% | |
| 100 mcg | 84.5% | 84.9% | |
| 125 mcg | 1.7% | 1.9% | |
| Surgical extent | Total thyroidectomy | Total thyroidectomy | |
| Histopathology | Colloid goiter (85.6%) | Colloid goiter (92.2%) | |
| Complications | | | |
| Temporary hypocalcemia | n=7 | n=10 | |
| Unilateral recurrent laryngeal nerve palsy | n=2 | n=0 | |

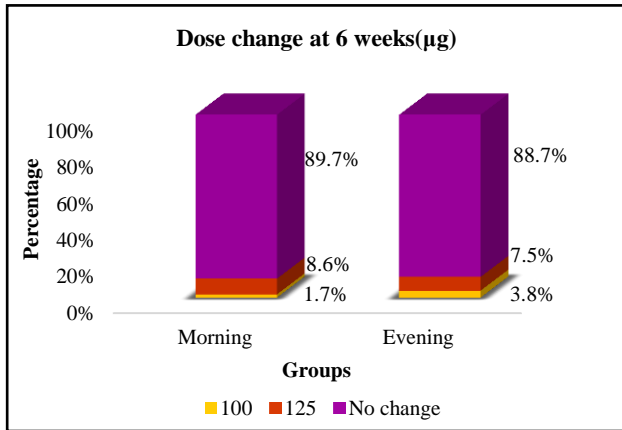


Figure 2: Comparison of levothyroxine dosage change at 6 weeks between 2 groups.

A major portion of our study population did not require change of dose of levothyroxine at 6 weeks with comparable results between the 2 groups. 89.7% in the early-morning group and 88.7% patients in the bedtime dose group did not require dose change. 8.6% of patients in early-morning group and 7.5% of patients in bedtime group required change to 125mcg respectively. 3.8% required change to 100mcg at 6 weeks interval in the bedtime group while only 1.7% required change to 100mcg in the morning group (Figure 2).

Primary outcome

- At 6th week assessment, mean TSH level of early-morning group (4.39±1.19 µIU/ml) and bedtime group (4.33±1.52 µIU/ml) did not show any statistical difference (p=0.06). At 12th week assessment mean TSH level of early-morning group (4.22±0.73 µIU/ml) and bedtime group (4.02±0.87 µIU/ml) did not show any statistical difference (p=0.08) (Figure 3).
- At 6th week assessment, mean fT₄ level of bedtime group (1.18±0.26 ng/dl) was higher than early-morning group (0.96±0.52 ng/dl), and the difference was not statistically significant (p=0.61). At 12th week assessment, mean fT₄ level of bedtime group (1.30±0.15 ng/dl) was higher than early-morning

group (0.93±0.09 ng/dl), and the difference was also statistically significant (p=0.0005) (Figure 4).

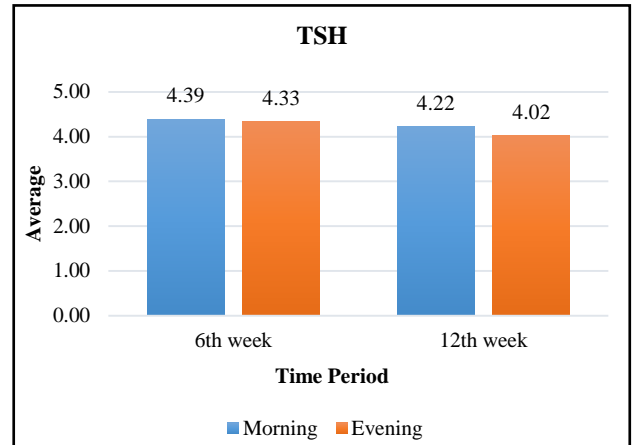


Figure 3: TSH levels at 6th & 12th week among 2 groups.

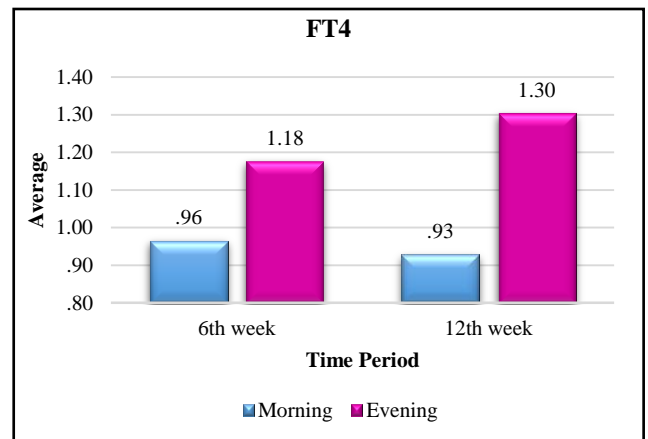


Figure 4: fT₄ levels at 6th and 12th week among 2 groups.

Secondary outcome

There was a small but insignificant decrease in BMI (body mass index) of the patients at 6 and 12 weeks, p value of 0.25 and 0.10 respectively (Table 2).

Table 2: Results at 6th and 12th weeks of early-morning versus bedtime levothyroxine groups.

| Characteristic (Mean-SD) | Early-Morning dose group | | | Bedtime dose group | | |
|--------------------------|--------------------------|--------------------|----------|--------------------|---------|----------|
| | Baseline | 6 weeks | 12 weeks | Baseline | 6 weeks | 12 weeks |
| BMI(kg/m ²) | 25.36 | 25.42 | 25.38 | 24.85 | 24.58 | 24.65 |
| TSH | 2.18 | 4.39 | 4.22 | 1.9 | 4.33 | 4.02 |
| fT ₄ | 1.36 | 0.96 | 0.93 | 1.45 | 1.18 | 1.30 |
| Characteristic | Mean of SD | | | P value | | |
| | Morning dose group | Evening dose group | | | | |
| BMI(kg/m ²) | 0.08 | 0.35 | 0.12 | | | |
| TSH | 0.17 | 0.31 | 0.077 | | | |
| fT ₄ | 0.036 | -0.13 | 0.0005 | | | |

DISCUSSION

After total thyroidectomy levothyroxine replacement has a narrow therapeutic index and is not only essential but also required lifelong. It has significant consequences for millions of people taking the drug on a daily basis. Intestinal absorption of levothyroxine is almost 60-80%.⁵ The small bowel is the principal site of levothyroxine absorption by a process of translocation across the mucosa that remains uncertain.⁶⁻⁸ There is a prolonged exposure of the levothyroxine to the intestinal wall due to slow bowel motility at night, resulting in improved uptake. When greater than regular dose is required to maintain TSH in the normal range in post total thyroidectomy patients, it's vital for the surgeon to find out the reason behind it. The usual reason for poor response to treatment is non-compliance. In post total thyroidectomy patients non-compliance is usually due to the requirement of levothyroxine to be taken early-morning in the empty stomach. Also, after taking levothyroxine, patients have to delay breakfast by an hour, including coffee or tea, to assure proper absorption of levothyroxine.

Unawareness of levothyroxine absorption may lead to continuous manipulation of its dosage among patients, termed as pseudomalabsorption. After ingestion, levothyroxine dissolution occurs in the stomach in the presence of gastric pH, with major absorption happening in the jejunioileal region in the first 90 minutes. This is the reason for the mandatory 1 hour gap between drug ingestion and food intake. Two important thyroid transporters have been studied in the absorption of thyroxine: MCT 8 (monocarboxylate transporter) and MCT 10. MCT 8 is responsible for the absorption across the blood brain barrier and MCT10 is expressed in the basolateral membrane of intestinal mucosa for absorption. Levothyroxine absorption has been noted to be influenced by sucralphate, iron sulphate, calcium preparations, aluminium antacids, bile acid sequestrants, ralexifen, vitamins and herbal remedies.^{9,10} The effect of proton pump inhibitors has been confirmed by TEARS study. A fibre rich diet has been shown to impede the intestinal absorption of levothyroxine.^{11,12} Many inactivating pathways of T₄ metabolism, like glucuronidation and sulphation in liver may have significant variation during the day, contributing to greater bioavailability at night.¹³ Consequently prevailing drug information resources and manufacturers advocate that levothyroxine is to be taken on an empty stomach in the morning.¹⁴⁻¹⁶

Our study showed no significant difference in TSH levels with the evening dose of levothyroxine as compared to the conventional morning dose. There was a small improvement in fT₄ levels noted with the bedtime dose in our study with no disturbance in the circadian rhythm. This helped us conclude that bedtime dose of levothyroxine would be convenient for those patients who miss their doses frequently due to their busy

schedule and to those children who have difficulty maintaining compliance. Our 6th week assessment showed no statistical difference in the mean TSH level of early-morning group (24.39±1.19 µIU/ml) and bedtime group (4.33±1.52 µIU/ml) (p=0.06). At 12th week assessment mean TSH level of early-morning group (4.22±0.73 µIU/ml) and bedtime group (4.02±0.87 µIU/ml) did not show any statistical difference (p=0.08). This finding is consistent with the study done by Bolk et al, Rajput et al but is in contrast to the study done by Bach-Huynh et al.²⁻⁴ Similarly, the mean fT₄ levels at 12th week assessment showed a significant statistical difference where the fT₄ levels were higher with the bedtime dose of levothyroxine. This was in agreement with above mentioned studies.^{2,3} There have been other studies stating that levothyroxine taken at empty stomach before breakfast is better compared to bedtime too.¹⁷ Owing to the limitations of the study, we could propose a bedtime dose of levothyroxine to those patients who were highly noncompliant as compared to skipping/alternate timing of the morning dose, stressing the necessity of further studies in this direction.

Lastly, there was no significant difference noted in the BMI with respect to the two regimes in our study. Weight gain and loss becomes a significant matter of concern for patients. An objective analysis of quality of life parameters was not conducted in our study. A study by Bolk et al in the past did not show any difference in quality of life in morning and bedtime dose of thyroxine, neither was there any change noted in lipid profile and creatinine levels.²

Limitations

A crossover trial would eliminate the necessity for controls as the patients would serve as their own controls, hence negating confounding factors. Inter subject variability could be another factor leading to bias. Quality of life assessment could prove advantageous and provide objective analyses of outcomes, which was not done in our study. Various other changes in biochemical parameters including lipid profile changes can provide an added advantage of change of levothyroxine intake time. Finally, a larger population with a longer duration of study would add more information and clarity as to the clear advantages of bedtime dose. This study was particularly done in post total thyroidectomy setting unlike other studies which were primarily designed for clinically hypothyroid patients. Therefore, we could only generalise the results for total thyroidectomy subjects, that the bedtime dose of levothyroxine is similar to early-morning dose if not better owing to nil variation in TSH and mild improvement in fT₄ levels.

CONCLUSION

There is a notable correction in fT₄ level with no significant variation of TSH when the same dose of levothyroxine was taken at bedtime as compared to early-

morning, keeping the circadian rhythm intact. Comparative metabolism and bioavailability was inferred with bedtime and early-morning dose of the drug.

Surgeons may consider replacing levothyroxine at bedtime as an alternative to the conventional early-morning dose in post total thyroidectomy patients with poor compliance as there was no variation of TSH in both the groups.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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