ORIGINAL ARTICLE

A Crossover Study Evaluating Effect of Timing of Levothyroxine on Thyroid Hormone Status in Patients of Hypothyroidism

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Abstract

Objective: Current literature shows a definite benefit of fasting state Levothyroxine administration. However, superiority of any specific timing is not yet established. Our study was designed to compare the effect of timing of levothyroxine administration, morning versus evening dose, on thyroid profile control in patients of hypothyroidism.

Methodology: A randomized double-blind crossover study was performed on 60 patients with primary hypothyroidism, euthyroid on stable levothyroxine regime of 100 µg daily, randomized into two sequence groups, morning dose first (AB sequence) versus evening dose first (BA sequence) with switch over after 6 weeks. Primary endpoints were change in thyroid function tests.

Results: There was an insignificant rise in TSH in morning dose first group (AB) at 6 weeks which reduced significantly in evening dose, [2.36(1.11) to 2.45(1.19) mIU/L (p=0.56)], [2.07(0.99) (p=0.006)] respectively. Levothyroxine evening dose first group (BA) showed significant reduction of TSH levels at 6 weeks followed by non significant increase [2.63(0.96) to 1.85(1.35) mIU/L, (p=0.002)], [2.14(1.16), (p=0.15)]. Group AB showed mild followed by significant rise in FT_4 at 6 and 12 weeks respectively, [1.06(0.30) to 1.14(0.33) ng/dl (p=0.18)], [1.24(0.36) (p=0.008)]. FT_4 of BA sequence significantly increased at 6 weeks followed by mild increase, [1.10(0.29) to 1.20(0.28) ng/dl (p=0.01)] [1.23(0.31) ng/dl (p=0.58)]. FT_3 of AB revealed initial reduction (p=0.87), followed by significant rise (p=0.02). Group BA showed a significant rise (p=0.04) in FT_3 followed by fall (p=0.63).

Conclusion: Bedtime dosing of Levothyroxine showed improved thyroid hormone status control and could be a viable option in treatment of patients with hypothyroidism

Introduction

Hypothyroidism, a commonly encountered disorder, is characterized by reduction in thyroid hormones. The effects of hypothyroidism are largely correlated with the severity of hormone deficiency whatever be the etiology.[1] The consistent potency and long half life of levothyroxine make it an ideal modality of treatment in Hypothyroidism.[2] The fact that the medicine has a very narrow therapeutic range,[3] an accurate adjustment is required for target Thyrotropin (TSH) controls. For a good control of thyroid function, compliance and adherence to accurate prescription instructions is important. However in the face of several factors influencing the absorption of the drug, the optimal drug effects may be altered.

There are no specific guidelines regarding timing of levothyroxine intake. Usual recommendations for the drug are that it should be taken on an empty stomach, usually in the morning, before breakfast. Studies have shown fasting conditions to be most suitable for consistent and optimal absorption of the drug, with higher and variable TSH levels when taken with breakfast.[4] The absorption of levothyroxine, occurring in the small intestine, may vary significantly to the tune of 50-80% being absorbed.[2] Strict instructions regarding taking levothyroxine on empty stomach, early morning may be associated with compliance issues. Patients' lifestyle and consumption of other medications advised to be taken empty stomach could make it inconvenient for the patients leading to failure to follow this advice. An alternative regimen for ideal timing of the drug needs to be reviewed.

We hypothesize that Thyroid hormone status is controlled better if Levothyroxine is administered in evening then in morning among patients of hypothyroidism. Hence our study was designed to compare the effect of timing of levothyroxine administration over thyroid profile control in the Indian Subcontinent.

Methodology

Study Design

A randomized double-blind crossover study was performed among patients with primary hypothyroidism who visited Medicine wards and Out-patient Department, S.M.S. hospital, Jaipur. Crossover study was ideal as Hypothyroidism is a chronic disease without permanent cure where treatment is given for symptomatic relief. In addition our study's objective was to evaluate a slight modification of standard treatment. Uniformity regarding sequence of treatment regimes and period was kept in this 2x2 crossover design. We did not keep washout period as same dose of same drug was given, but only on different time of the day.

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Table 1: Baseline characteristics of patients: Mean (SD)

Variable	Group AB	Group BA	Test statistics	P value
Age (in years)	39.70 (11.77)	39.72 (14.02)	0.006	0.99
Sex: Male	2	4		
Female	28	25		
FT_3 (pg/mL)	4.07 (0.98)	3.93 (0.87)	0.58	0.56
FT_4 (ng/dL)	1.06 (0.30)	1.10 (0.29)	-0.52	0.61
TSH (mIU/L)	2.36 (1.11)	2.63 (0.96)	-0.99	0.33
BMI (kg/m^2)	23.84 (2.16)	24.65 (1.97)	-1.5	0.14
Lipid profile: TG (mg/dL)	146.28 (47.80)	127.44 (53.03)	1.43	0.16
TC	192.40 (45.42)	172.50 (39.97)	1.78	0.08
HDL	44.73 (4.80)	45.77 (5.11)	0.81	0.42
LDL	113.44 (45.25)	101.43 (34.45)	1.14	0.26
S. Creat (mg/dL)	0.93 (0.20)	0.99 (0.17)	1.24	0.22

Table 3: Comparison of mean of difference at (between 6 and 12 weeks) of variables in two sequence groups

Variables	Mean of difference (SD)		t Statistics	*P* Value
	Group AB	Group BA		
TSH (mIU/L)	0.38 (0.70)	-0.29 (1.07)	2.86	0.006
FT3 (pg/mL)	-0.48 (1.06)	-0.08 (0.92)	-1.54	0.13
FT4 (ng/dL)	-0.10 (0.19)	-0.03 (0.30)	-1.07	0.29
BMI (Kg/m^2)	-0.08 (0.25)	-0.04 (0.14)	-0.76	0.45
TC (mg/dL)	3.31 (29.08)	-10.87 (26.76)	1.95	0.06
TG (mg/dL)	3.86 (26.48)	2.98 (55.34)	0.08	0.94
LDL (mg/dL)	7.11 (32.22)	-8.64 (43.15)	1.59	0.12
HDL(mg/dL)	-1.09 (8.40)	-0.40 (5.72)	0.37	0.71
S. Creatinine (mg/dl)	0.05 (0.17)	-0.003 (0.12)	1.38	0.17

Group AB – Morning Dose First Group; Group BA – Evening Dose First Group

Table 2: Results of two sequence groups at baseline, 6 weeks, 12 weeks: Mean (SD)

Variable	Group – AB (n=30) (Morning dose 1st group)			Group – BA (n=29) (Evening dose 1st group)		
	Baseline	6 weeks	12 weeks	Baseline	6 weeks	12 weeks
TSH (mIU/L)	2.36 (1.11)	2.45 (1.19)	2.07 (0.99)	2.63 (0.96)	1.85 (1.35)	2.14 (1.16)
FT4 (ng/dl)	1.06 (0.30)	1.14 (0.33)	1.24 (0.36)	1.10 (0.29)	1.20 (0.28)	1.23 (0.31)
FT3 (pg/ml)	4.07 (0.98)	3.98 (1.21)	4.46 (0.52)	3.93 (0.87)	4.34 (0.77)	4.42 (1.04)
BMI (Kg/m^2)	23.84(2.16)	23.89(2.22)	23.97(2.19)	24.65(1.97)	24.76(1.90)	24.80(1.95)
TC (mg/dl)	192.40(45.42)	188.09(36.87)	184.78(34.94)	172.50(39.97)	174.52(35.00)	185.39(31.40)
TG (mg/dl)	146.28(47.80)	142.61(42.74)	138.74(37.97)	127.44(53.03)	137.61(57.82)	134.62(61.79)
LDL (mg/dl)	113.44(45.25)	109.09(38.91)	102.00(39.69)	101.43(34.49)	95.18 (34.24)	103.82(49.49)
HDL (mg/dl)	44.73 (4.80)	46.68 (6.00)	47.77 (6.09)	45.77 (5.11)	47.66 (4.49)	48.06 (4.74)
S. Creatinine (mg/dl)	0.93 (0.20)	0.98 (0.15)	0.94 (0.17)	0.99 (0.17)	0.93 (0.20)	0.93 (0.19)

Study population

Inclusion criteria consisted of patients of primary hypothyroidism of age 18 years or more, who were euthyroid on stable levothyroxine regime of 100 µg daily for at least 6 months. Pregnant females, patients suffering from gastrointestinal disease and those on medication known to interfere with the uptake of Levothyroxine were excluded. Patients were taken for study after taking informed consent. The medical ethics committee of the S.M.S. Hospital, Jaipur, approved the study protocol.

Study protocol

60 patients satisfying inclusion criteria were randomized into one of the two sequence groups of 30 each, one group taking 100µg levothyroxine in the morning and placebo at bedtime (Morning Dose First Group which we will refer to as "AB sequence group"), and the other group taking levothyroxine at bedtime and placebo before breakfast (Evening Dose First Group which we will refer to as "BA sequence group"). Patients were instructed to take morning dose at least one hour before breakfast and bedtime dose at least two hours after dinner with plain water. Folic acid tablets of 5mg strength, which had appearance similar to levothyroxine tablets were used as placebo. After 6 weeks, patients in the Morning Dose First Group were switched to placebo in the morning and levothyroxine at bedtime for next 6 weeks. Similarly, after 6 weeks, patients in Evening Dose First Group were shifted to levothyroxine in the morning and placebo at bed time for another 6 weeks.

Patients' assessment

Patients were assessed at baseline, 6 weeks and 12 weeks. Clinical examination including Body Mass Index and biochemical parameters were conducted on each visit. Blood samples were drawn on the morning of the every planned visit and patients were instructed not to withhold levothyroxine tablets on the day of blood sampling. Blood samples were collected after overnight fasting and analyzed for Thyrotropin (TSH), free triiodothyronine (FT_3), free thyroxine (FT_4), serum creatinine and lipid Profile. All tests were done in Central Laboratory, S.M.S. Hospital, Jaipur.

Patients' data was collected at every planned visit, and was analyzed at the end of study.

Laboratory methods of estimation of parameters

Total cholesterol, triglycerides, high density lipoprotein were estimated using Beckman Cx4 auto analyzer. LDL cholesterol was calculated using Friedewalds formula. Chemiluminescent assay with fully automated Immunolyte 2000 machine in Thyroid lab of SMS Hospital was used for measurement of FT_3, FT_4, and TSH level.

Statistical analysis

The Primary aim of the study was to see the change occurring in Thyrotropin and Thyroid hormone levels when levothyroxine was taken at bedtime versus in the morning. The effect of bedtime Vs morning regime of levothyroxine on serum creatinine, lipid levels and Body Mass Index constituted the secondary objective of the study.

The direct treatment effect among primary end points was measured by performing an independent t test between the differences of 6 and 12 weeks in the AB sequence group (levothyroxine morning dose first) and the BA sequence group (levothyroxine evening dose first). The presence of carryover effect from one period to other was measured by performing an independent t test on sum of the variables at 6 weeks and 12 weeks. All p values were two sided.

Baseline characteristics of two sequence groups were analyzed. For count data chi-square test was used and independent t test was used for continuous data.

Results

One out of 30 cases in Evening dose first group (BA) was lost to follow up and excluded from analysis, while all 30

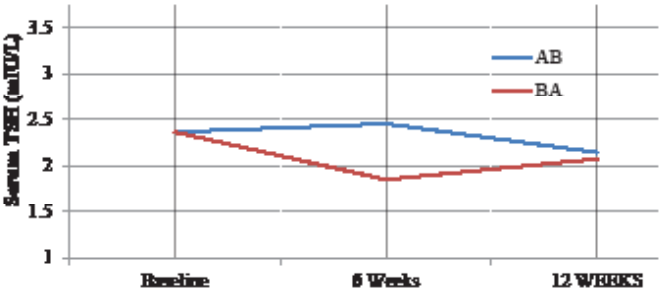

Fig. 1: Comparison serum TSH between two groups at baseline, 6 weeks and 12 weeks (Group AB – Morning dose first group; Group BA – Evening dose first group).

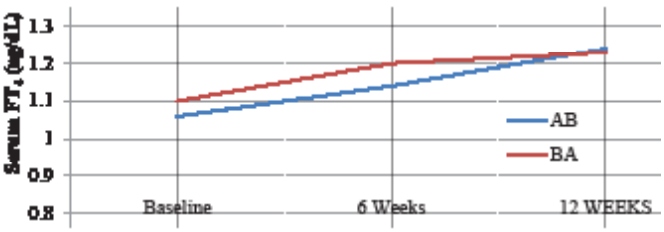

Fig. 2: Comparison of serum FT_4 between two groups at baseline, 6 weeks and 12 weeks (Group AB – Morning Dose First Group; Group BA – Evening Dose First Group).

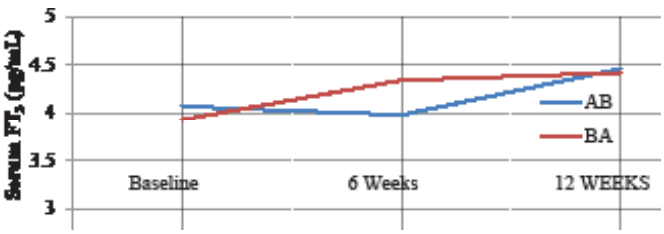

Fig. 3: Comparison of serum FT_3 between two groups at baseline, 6 weeks and 12 weeks (Group AB – Morning dose first group; Group BA – Evening dose first group)

cases from AB group remained in the study till end. Baseline characteristics including BMI of both the sequence groups were comparable (Table 1).

Primary outcomes: (Table 2, 3)

Within group and Inter group Analysis

1. Mean(SD) Thyrotropin levels (mIU/L): Levothyroxine morning dose first group, showed a non significant rise in Mean (SD) Thyrotropin levels (mIU/L) from 2.36 (1.11) to 2.45 (1.19) mIU/L (p=0.56) at 6 weeks but when changed over to evening doses, levels reduced significantly from 2.45 (1.19) to 2.07 (0.99) (p=0.006) at 12 weeks. Levothyroxine evening dose first group showed a significant reduction of Mean (SD) TSH levels (mIU/L) from 2.63 (0.96) to 1.85 (1.35) mIU/L, (p=0.002) in first 6 weeks. On switching over to morning doses, there was a non significant increase in levels from 1.85(1.35) to 2.14(1.16), (p=0.15) (Figure 1).

   Intergroup comparison of Mean of difference of TSH at the end of 6 weeks (p=0.002) and 12 weeks were statistically significant (p=0.006).

2. Mean (SD) FT4 (ng/dl) levels: Group AB showed a negligible increase in Mean (SD) FT_4 (ng/dl) levels, from 1.06(0.30) to 1.14(0.33) ng/dl (p=0.18) at 6 weeks but on crossover to evening doses, FT_4 levels significantly increased from 1.14 (0.33) to 1.24 (0.36) at 12 weeks (p=0.008). Group BA showed a significant increase in FT_4 from 1.10(0.29) to 1.20(0.28) ng/dl (p=0.01) at 6 weeks when on evening Levothyroxine dose, which on crossover to morning dose regimen, resulted in a mild increase to 1.23(0.31)ng/dl at 12 weeks(p=0.58) (Figure 2).

3. Mean (SD) FT3 levels (pg/ml): Group AB, revealed a negligible reduction from 4.07(0.98) to 3.98(1.21) pg/ml (p=0.87). On crossover to evening levothyroxine regimen FT_3 significantly increased (p=0.02). Group BA showed a significant rise in FT_3 when they were on evening doses from 3.93(0.87) to 4.34(0.77) (p=0.04). On crossover to morning doses, FT_3 levels decreased slightly, (p=0.63) (Figure 3).

Direct Treatment and Carryover effect of 2 sequence groups (Morning versus Evening groups)

Pre test done using two sample Independent t test on sum of variables at 6 weeks and 12 weeks revealed that there was a negligible carryover effect (p=0.42, 0.77 and 0.34) respectively for FT3, FT4, TSH. The independent t test done for differences between treatment effect of both the groups revealed that Evening dose group had significantly better control of TSH then Morning dose group with a mean difference of 0.66 mIU/L (confidence interval 0.19 to 1.13) (p=0.006). (Table-3) but there was no significant difference in FT3 (p=0.13) and FT4 level (p=0.29) in both groups.

Secondary outcomes

BMI: Both the sequence groups (AB and BA) showed a mild but insignificant increase in BMI (P= 0.32, 0.08 respectively). Serum creatinine did not show any significant variation in both the groups. On analyzing changes in triglycerides, total cholesterol, serum HDL, serum LDL in each group at 6 and 12 weeks the difference was found to be statistically insignificant. Intergroup analysis also showed insignificant difference.

Discussion

Current literature shows a definite benefit of fasting state Levothyroxine ingestion over non-fasting state, but superiority of any specific timing of Levothyroxine administration over other is not yet established. It is consistently inferred that whatever be the timing of Levothyroxine, it should be well separated from meal times, it should not need much change in patients routine lifestyle and food practices and it should not interfere with other drugs the patient may be taking. In this regard, bedtime Levothyroxine intake could be more convenient for many patients, as they do not have to postpone breakfast and can easily adjust intake of other medications to be taken on empty stomach.

The benefit of cross-over design adapted in our study was that it avoids the problem of comparability of cases and control with regards to confounding variables as each crossover case becomes his/her own control. The inter subject variability issue is overcome in this design.

Only those patients who were stable on 100 µg levothyroxine for at least past 6 months were included in our study so as to exclude the variability occurring due to dose differences. In addition, individual patient's response to medications may vary, so new patients were excluded and only those who were well controlled with the levothyroxine were selected.

Elimination of these confounding variables brought precision for evaluating direct treatment effects of bedtime versus morning dosages.

The improvement of thyroid function tests when on evening dose of Levothyroxine observed in our study could be explained by several factors. The pulsatile nature of TSH release with maximum levels at night[5] favors bedtime levothyroxine supplementation. Physiologically, a high nocturnal gastric acid secretion[6] would lead to better drug absorption at night. Also, reduced gut motility gives more time for absorption at this time improving its bioavailability.[7] The patients when on evening dose were instructed to take levothyroxine at least two hours post dinner. This was not difficult for many as not ingesting anything after dinner was customary for them. Also, there would be ample time for drug absorption at night. Contrary to this, in the morning, patients tend to have morning tea or coffee and an early breakfast is also a routine for many. Our patients were instructed to remain fasting for one hour following morning levothyroxine ingestion.

Reviewing literature we find similar results in some studies investigating the effects of timing of levothyroxine on thyroid profile. Effect of timing of levothyroxine, investigated by Nienke Bolk et al in a randomized double blind crossover study[8] revealed definite benefit with bedtime levothyroxine dose resulting in a significant fall in Thyrotropin levels and an increase in free thyroid hormone levels with bedtime doses. These results are consistent with the favourable outcome of evening dose levothyroxine obtained in our study. Elliot DP conducted a retrospective review of data in 15 elderly residents of a nursing home who underwent a change in timing of levothyroxine from morning to midnight.[9] They found a reduction in TSH following night time dosage of levothyroxine which was however, not significant statistically. The author concluded the possibility of post breakfast levothyroxine administration.

Another study comparing morning and evening dose of levothyroxine was conducted by Rajesh Rajput et al [10]. The authors included newly diagnosed patients of primary hypothyroidism and observed the thyroid hormone status, and quality of life parameters following treatment with levothyroxine in morning and evening time dosages. Similar dose requirement in both groups of patients to achieve normal thyroid hormone status was observed. Their study concluded that evening dose administration of levothyroxine could be an effective alternative to the usual practice of morning dosage. However, not all studies showed a benefit with evening dose levothyroxine. Thein-Giang Bach-Huynh et al studied the thyroid hormone status achieved with levothyroxine dosing taken on empty stomach, along with breakfast and at bedtime.[11] Best results of Thyrotropin control were seen when levothyroxine was taken in fasting conditions as compared to when taken with food or at bedtime. They found variability in control of thyroid profile with levothyroxine taken in other than fasting states. Another recent study comparing Thyrotropin levels when taken fasting as compared to with breakfast[4] also reported variability in TSH levels and requirement of closer observation in patients taking levothyroxine with breakfast.

Quality of life parameters are of importance in management of hypothyroidism. No objective evaluation was done in this regard in our study and biochemical parameters were mainly considered. This aspect was studied by Nienke Bolk et al where they did not find any difference in quality of life in patients with morning or evening dose of levothyroxine.[8] Changes in BMI did not show any difference in both the regimes in our study. As seen in clinical practice, while dealing with patients of hypothyroidism, reduction or gain of weight is an important matter of concern for the patient. Other parameters including lipid profile and serum creatinine levels did not show any difference in both the groups.

Conclusion

Considering a better biochemical thyroid hormone status control and the secondary outcomes not showing any adverse changes gives us encouraging ground to consider bedtime doses of levothyroxine administration as a viable option. In the present scenario with an extremely busy and fast morning lifestyle schedule, bedtime doses could prove to be very convenient and be instrumental in improving compliance. Also, patients who are not adequately controlled with morning dose levothyroxine could be shifted to bedtime doses for a better Thyrotropin reduction. Further studies including larger patient population and for longer duration need to be conducted to establish whether these beneficial effects sustain for long duration.

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