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Research Article

# A Study Protocol on Daily Verses Weekly Levothyroxine Therapy in Hypothyroid Subjects

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## Abstract

India has high prevalence of hypothyroidism (10%) and daily levothyroxine (LT4) therapy is complicated with non-compliance issue which can lead to metabolic and cardiovascular risk [1,2]. 42 million people in India suffer from thyroid diseases [3]. According to a recent study done in 2013, India has high prevalence of hypothyroidism, which affects 1 in 10 people [4]. Untreated hypothyroidism can lead to goiter, heart problems, mental health issues, peripheral neuropathy, myxedema, infertility and birth defects [4]. The recommended and appropriate replacement therapy for hypothyroidism is levothyroxine.

Levothyroxine is needed to be taken while fasting on a daily basis. Various reports have highlighted about 80% non-compliance with daily long term use of levothyroxine in hypothyroid patients [5]. In adults, non-compliance with daily levothyroxine can lead to metabolic and cardiovascular risk disturbances. Hence, the need of the hour is to improve the compliance of levothyroxine. Levothyroxine has an elimination half-life of about 7 days. Levothyroxine (LT4) is a pro-hormone and it gets peripherally converted to T3 (tri iodothyronine), the biologically active hormone and this conversion process is auto regulated in the body. Hence, once weekly thyroid hormone administration can be scientifically justified and would be expected to result in higher compliance in hypothyroid management.

We propose to undertake a cohort study of 50 participants, who are established hypothyroid subjects on daily LT4 therapy. Groups will be equally divided to receive either daily or weekly doses of LT4 for 24 weeks. Thyroid hormone parameters, hyperthyroid symptoms, ECG and liver enzymes will be measured at baseline and after 12 and 24 weeks. If the outcome variables in both groups are comparable whilst maintaining euthyroid state, weekly LT4 therapy may come out as a better strategy to improve compliance in hypothyroid patients. The primary outcome measure for effectiveness would be serum TSH. Secondary efficacy variables would be serum fT4, FPG, Creatinine, SGOT, SGPT, Complete hemogram, clinical changes by the hyperthyroidism symptom scale (HSS), biochemical impact of weekly LT4 with the thyroid function test, ECG, compliance from subject record diary and safety assessed in terms of treatment emergent adverse events and routine hematological and biochemical test.

Data would be analyzed in the Department of Endocrinology, K.P.C Medical College and Hospital.

***Keywords:*** *Levothyroxine (LT4); Hyperthyroidism Symptom Scale (HSS); Hypothyroidism*

## Introduction

India has high prevalence of hypothyroidism (10%) and daily levothyroxine (LT4) therapy is complicated with non-compliance issue which can lead to metabolic and cardiovascular risk [1,2]. 42 million people in India suffer from thyroid diseases [3]. According to a recent study done in 2013, India has high prevalence of hypothyroidism, which affects 1 in 10 people [4]. Untreated hypothyroidism can lead to goiter, heart problems, mental health issues, peripheral neuropathy, myxedema, infertility and birth defects [4]. We propose to undertake

a cohort study of 50 hypothyroid subjects on daily LT4 therapy hypothyroidism subjects, equally divided to receive either daily or weekly doses of LT4 for 24 weeks and undertake assessment of efficacy, compliance and safety of weekly levothyroxine treatment in hypothyroidism.

## Aims and Objectives

**Primary outcome variable:**

1. Assessment of Serum TSH.

**Secondary outcome variables:**

1. Assessment of serum fT4, FPG, Creatinine, SGOT, SGPT
2. Assessment of Complete hemogram
3. Assessment of clinical changes by the hyperthyroidism symptom scale (HSS)
4. Assessment of biochemical impact of weekly LT4 with the thyroid function test at baseline as well as 4 hours after LT4 administration
5. Assessment of ECG at baseline as well as 4 hours after LT4 administration
6. Assessment of compliance from subject record diary
7. Assessment of Quality of Life from SF-8
8. Safety assessed in terms of treatment emergent adverse events and routine hematological and biochemical test.

## Materials and Methods

**Study area:** Endocrinology OPD in the KPC Medical College and Hospital, Kolkata.

**Study population**: Adult subjects, aged between 18 - 60 years, with diagnosed hypothyroidism. Further selection criteria have been mentioned later.

**Study period:** The study is intended to be completed within a period of 1½ years from inception. Subject recruitment is expected to be completed within the first 12 months.

**Sample size:** A convenient sample size of 50.

### Parameters to be studied

1. **Primary outcome variable:**
    - Assessment of Serum TSH on days 0, 84 and 168.
2. **Secondary outcome variables:**
    - Assessment of serum fT4, FPG, Creatinine, SGOT, SGPT days 0, 84 and 168.

- Assessment of Complete hemogram on days 0, 84 and 168.
- Assessment of clinical changes by the hyperthyroidism symptom scale (HSS) (6) at baseline as well as 4 hours after LT4 administration on days 0, 84 and 168.
- Assessment of biochemical impact of weekly LT4 with the thyroid function test at baseline as well as 4 hours after LT4 administration on days 0, 84 and 168.
- Assessment of ECG at baseline as well as 4 hours after LT4 administration on days 0, 84 and 168.
- Assessment of compliance from subject record diary on days 0, 84 and 168.
- Assessment of Quality of Life from SF-8 on days 0, 84 and 168.
- Safety assessed in terms of treatment emergent adverse events and routine hematological and biochemical test.

### Study medication

The group G1 will be receiving their routine daily dose of LT4 medication. The group G2 will be taking a weekly dose equivalent to 7 times their daily dose of LT4. The marketed weekly formulations of weekly once LT4 (Sun Thyroid) are 25 mg, 50 mg, 75 mg and 100 mg. Participants may also be taking a combination of the above mentioned doses if required.

### Study technique

The study will commence only on approval of K.P.C Medical College Ethics Committee. It will conform to the Declaration of Helsinki for biomedical research involving human subjects and strict adherence to ICMR guidelines for clinical research would be maintained. Written informed consent would be obtained from all participants.

**Selection (eligibility) criteria are as follows:**

### The inclusion criteria

1. Individuals suffering from hypothyroidism
2. Age between 18 - 60 years
3. Gender: both male and female
4. Individuals with stable LT4 dose in the previous 3 months.
5. Baseline serum TSH.

**The exclusion criteria:**

1. Children i.e. patients < 18 years.
2. Pregnant and lactating women.
3. Individuals suffering from cardiac, liver or renal problems or any other chronic diseases.

4. History of substance abuse.
5. Any other condition which can lead the study investigators to consider the subject unsuitable for selection.
6. Patient participating in any other clinical study or have participated in the last three months.
7. Concomitant use of psychotropic drugs.
8. Concomitant serious disease of vital organs such as the liver, kidney, heart or lungs.
9. Patients who show any of the following values at the baseline laboratory tests: Hemoglobin < 9 g/dL, total leukocyte count < 3,000/$mm^3$, platelet count < 75,000/$mm^3$, AST and ALT ≥ 100 IU/L, Creatinine ≥ 1.5 mg/dL The blood tests should have been done not more than 4 weeks prior to enrollment.

### Procedures at different visits

1. 200 participants already on drug therapy will be recruited. They will be divided into two groups-G1 (n = 100) and G2 (N = 100)
2. On day 0, 24 hours after their last dose of LT4, all participants will be submitted to blood testing in fasting state (FT4, TSH, FPG, Creatinine, SGOT, SGPT, Complete haemogram), after which they will receive LT4 [5].
3. Participants in G1 will be advised to keep the usual daily dose (basic daily dose) of LT4. Participants in G2 will be advised to stop their usual daily dose and start taking weekly dose of LT4, equivalent to the total weekly dose, starting from day 0. All participants will maintain this treatment for 24 weeks.
4. After 12 weeks, on day 84, participants will again undergo the same blood tests in fasting state.
5. In both groups LT4 brands will not be changed and doses will also not be altered during the daily or weekly therapeutic regimens.
6. After 24 weeks, on day 168, all participants will again undergo the same blood tests in fasting state.
7. ECG and thyroid function test will be performed before and 4 hours after LT4 administration, on days 0, 84 and 168 in both groups.
8. At the end of the study (day168) all participants will be advised to go back to taking LT4 daily in their basic daily dose.

## Result

### Plan for analysis of data

Data would be summarized by routine descriptive and analytical statistics. Numerical variables would be analyzed for distribution by Kolmogorov-Smirnoff goodness-of-fit test and compared between groups by Student's unpaired t test, if normally distributed, or by Mann-Whitney U test, if otherwise. Fisher's exact test or Pearson's Chi-square test would be employed for intergroup comparison of categorical variables. The comparison of the normally distributed numerical variables at 3 points would be Repeated Measures ANOVA and by performed by Friedman's ANOVA if otherwise with Dunn's Multiple Comparison Test as Post hoc test. All analyses would be 2-tailed. Statistically significant would imply $p < 0.05$.

## Discussion

In spite of being easily treatable using a daily dose of levothyroxine (LT4), many patients remain hypothyroid. Many studies have shown that up to 40% of patients are undertreated, and also up to 40% may be overtreated, especially in the elderly. A study evaluating 339 hypothyroid patients aged 65 and over showed that more than 40% had low and 16% had high TSH levels, possibly correlated with lower weight .An interesting study performed in Brazil involving decompensated hypothyroid patients showed that more than 80% of the subjects said they did not follow physician instructions due to prescription misunderstanding or forgetfulness. A study conducted by Bach-Huynh and cols, evaluating alternative schedules for LT4 dosing, showed that administration while fasting remains the best option. Nevertheless, bedtime or breakfast schedules also showed satisfactory results and could be attempted in non-compliant patients. Some recent series evaluating hypothyroid patients with poor control have shown that adequate thyroid hormone levels were obtained after introducing weekly LT4 [6].

## Conclusion

Levothyroxine is needed to be taken while fasting on a daily basis, making compliance an important issue for proper therapeutic management. Various reports have indicated that non-compliance with daily long term use of levothyroxine in hypothyroid patients can lead to metabolic and cardiovascular risk . We propose to evaluate the effect of weekly doses of LT4 for 24 weeks and undertake assessment of efficacy, compliance and safety in a cohort study of 50 hypothyroid subjects on daily LT4 therapy hypothyroidism subjects.

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