ORIGINAL ARTICLE

Comparison Between Weekly vs Daily Dosing L-thyroxine for the Treatment of Hypothyroidism in Ramadan – A Pilot Randomized Controlled Trial

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ABSTRACT

Introduction: Muslims find it difficult to take L-thyroxine on empty stomach during Sahur. Furthermore, physiological changes during Ramadan alter thyroid hormones level. Objective: To compare the efficacy, safety and patient's preference of weekly vs daily dosing of L-thyroxine in Ramadan. **Method:** This is a pilot randomized open-label controlled trial among hypothyroid patients during Ramadan 2017-2018. Patients were randomized into weekly and daily arm. Weekly arm took 7x their usual L-thyroxine dose at least 30 minutes pre-sahur once a week while daily arm took their usual daily dose at least 2 hours after the last meal before bed. Thyroid hormones, lipid profile, cardiac parameters, cognitive and psychological function were assessed at baseline and at week 4. Cardiac reassessment was done within 24hrs after weekly dosing at week 2. **Results:** Eighteen patients were randomized into weekly and daily arm. Majority (66.7%) were hypothyroid secondary to radioiodine therapy. At the end of study, there were no significant changes of thyroid hormones level for weekly arm. However there was significant increment of TSH observed in daily arm [TSH w0 1.8(0.23,5.57) vs w4 3.65(0.45,16.1);p =0.011]. In terms of toxicities, there were no hyperthyroid or cardiac toxicities observed despite the significant increment of fT4 within 24hours of weekly dosing [fT4 w0 13.21(8.19,14.63) vs w2 17.43(12.38,22.55);p=0.011]. All patients were euthyroid and had no side effects. Majority (83.3%) of patients preferred weekly dosing during Ramadan. **Conclusion:** Weekly levothyroxine dosing during Ramadan appeared to be safe, efficient and the most preferred dosing method.
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Keywords: : L-thyroxine, Weekly dosing , Ramadan

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INTRODUCTION

Hypothyroidism, a common endocrine disorder, also affects Muslims who fast during the month of Ramadan. However, to date, guidelines and recommendations on management of hypothyroidism and Levothyroxine (L-thyroxine) replacement during Ramadan are scarce. L-thyroxine should be taken on empty stomach to ensure optimal absorption. During Ramadan, changes in gastric motility (due to prolonged fasting), interference with heavy meals, possible alteration in the circadian rhythm and the effect of the deiodinase activity might alter the absorption and metabolism of the L-thyroxine in the body (1). Apart from physiological changes, patients may also find it difficult to wake up early just to administer L-thyroxine on empty stomach before sahur (2). This will lead to medication compliance issue. Previous study on drug intake during Ramadan has observed more than 50% of patients were not comply to drug intake and some even stop taking their medications during Ramadan (3). Both factors (physiological changes and non-compliance) may contribute to suboptimal L-thyroxine replacement in hypothyroid patients during Ramadan. Weekly L-thyroxine is a feasible option to improve compliance and to ensure adequate replacement

during Ramadan. L-thyroxine has a long half life and it has an auto regulatory conversion from T4 (thyroxine) to T3 (triiodothyronine) in which conversion to active hormone increases at a low T4 level and decreases at a higher T4 level (4). Weekly L-thyroxine dosing has been investigated as an alternative regime to overcome non-adherence. Grebe et al (1996) found that weekly administration of L-thyroxine causes slight increment of TSH level. However patients remained euthyroid and there was no evidence of thyroxine toxicity reported (5). The objectives of this study are to compare the efficacy, side effects and patient's preference of weekly vs daily L-thyroxine replacement for Muslims in the month of Ramadan. This is a pilot randomized open labelled controlled trial conducted during Ramadan 2017 and 2018 involving hypothyroid patients who took weekly vs daily L-thyroxine . Data on efficacy (serum thyroid stimulating hormone (TSH) levels, free T4 levels and T3 levels changes), cardiovascular side effects, cognitive and psychological dysfunction, lipid parameters and patient's preferences were collected. Comparative analysis on efficacy, side effects and patient's preference of weekly and daily L-thyroxine dosing were evaluated.

MATERIALS AND METHODS

This is a randomized, open label, parallel two arm trial that was conducted in Ramadan 2017 and 2018. This study involved hypothyroid patients from two tertiary centres in east Malaysia. This study was approved by the Malaysia Medical Research and Ethics Committee (NMRR-17-621-34080)

Subject Recruitment

A total of sixty one patients were invited to join this study, however only twenty two patients were interested and consented. They underwent screening process which includes symptoms, cognitive, psychological assessment, blood investigations (thyroid hormones, lipid profile) and cardiac screening (electrocardiography, echocardiography, 24-hours Holter monitoring). Patients with ischemic heart disease, high Framingham cardiovascular risk score, cardiac abnormalities and pregnant women were excluded from this study. Four out of twenty two patients were excluded after screening. Total of eighteen patients who fulfilled the inclusion and exclusion criteria were randomized via simple randomization (drawing lots) into two arms; weekly and daily arm. The calculated sample size was based on the study by Grebe et al, Treatment of hypothyroidism with once weekly thyroxine using the means of T4 at 24hrs with G1(daily) 246pg/dl ± 25 and G2 (weekly) 285pg/dl ± 42, respectively. The calculated sample size is 13 subjects in each arm.

Study Protocol

During the first day of Ramadan, patients in the weekly arm were instructed to take seven times (7x) their usual L-thyroxine dose at least 30 minutes before sahur once a week while patients in the daily arm took their usual dose of L-thyroxine daily at least two hours after their last meal before bed.

Patients were assessed using Billewicz and Zulewski's score for hypothyroidism and Wayne's score for hyperthyroidism, cognitive assessment via Mini Mental State Examination (MMSE) and psychological assessment using DASS21 scoring system. Ten mililitres (10 mls) of blood samples were taken on each visit to analyse the level of thyroid stimulating hormone (TSH), free thyroxine (free T4), free triiodothyronine (free T3) and lipid profile using immune-enzymatic assay. All blood samples were taken in the morning where biologic variation does not influence diagnostic interpretation.
Clinical and laboratory assessment were done at baseline prior starting study (week 0) and at week 4 for both arms. Cardiac assessment which includes Electrocardiogram (ECG) and 24-hours ambulatory HOLTER were done at baseline (week 0) and were repeated (only for weekly arm) at week 2 (24-hours within the weekly L-thyroxine administration for cardiac toxicity detection). Patient's diaries were reviewed at every visit to ensure compliance and during the last visit (week 4) patients preferred dosing method were assessed. The visit and procedures flow is shown in Figure 1

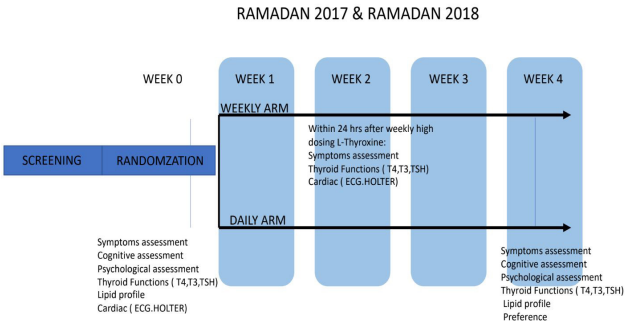

Figure 1: Visit and Procedures flow

STATISTICS

The data collected were analysed using SPSS version 24. As the data was not normally distributed, Median is used to described the data. Median difference between week 0 (baseline prior study) & week 4 (end of Ramadan) of each thyroid hormones (T4,T3,TSH) were analyse via Wilcoxon Signed Rank Test which is a paired non parametric test to look for significant change of hormones at the end of study while the median level of thyroid hormones at the end of study between both arm were compared via Mann Whitney U Test .

RESULT

Baseline Characteristic

Majority of the patients were female in both arms with median age between 34-45 years old. Most of the patients were hypothyroid secondary to radio-iodine therapy with median duration of illness between two to three years and median dose of L-thyroxine 100mcg/

day. Both arms have comparable thyroid hormones, lipid and cardiac parameters at baseline as described in Table I.

Table I Baseline Characteristics

Median (IQR)	Weekly (n=9)	Daily (n=9)	P Value
Age (years)	34(27.5,48.5)	45(36.5,51)	0.222
Gender (number,%)			
Female	8 (88.9%)	7 (77.8%)	0.52
Male	1 (11.1%)	2 (22.2%)	
Illness duration (yrs)	3(0.5,8)	2(0.8,7)	0.796
Etiology (number,%)			
Post RAI	(66.7%)	6 (66.7%)	1.0
Post-Surgery	1 (11.1%)	1 (11.1%)	
Autoimmune	2 (22.2%)	2 (22.2%)	
fT3 (pmol/L)	5(4.2,5.35)	5(4.0,5.4)	0.796
fT4 (pmol/L)	13.21(8.19,14.63)	14.48(11.58,16.14)	0.222
TSH (mIU/L)	2.63(1.0,7.36)	1.8(0.23,5.57)	0.340
L-hyroxine(mcg/day)	100(62.5,100)	100(75,125)	0.605
Systolic BP (mmHg)	117(110,134)	116(104,120.5)	0.340
Diastolic BP (mmHg)	71(64,77.5)	71(66.5,80.5)	0.666
Weight (kg)	54(49.2,67.8)	73.9(53.3,78.40)	0.136
T. Cholesterol (mmol/L)	5.4(4.7,6.0)	5.5(5.05,6.9)	0.387
LDL (mmol/L)	3.35(2.99,3.88)	3.79(3.07,4.23)	0.605
HDL (mmol/L)	1.39(1.08,1.78)	1.47(1.38,1.78)	0.546
Triglyceride (mmol/L)	1.1(0.85,1.2)	1.00(0.65,1.85)	0.931
Heart Rate (bpm)	71(65.5,73.5)	74(67,83.5)	0.540

Legend: RAI=Radioactive Iodine, fT3=triiodothyronine, fT4=thyroxine,TSH=thyroid stimulating hormone, TLDL=Low Density Lipoprotein, HDL=High Density Lipoprotein

Efficacy – Thyroid Hormones

Figure 2 depicts the changes of thyroid hormones (fT3, fT4, TSH) at week 0 and week 4 of Ramadan. There were no significant change of all thyroid hormones at the end of study in weekly arm however there was a significant increment of TSH observed in daily arm [TSH w0 1.8(0.23,5.57) vs w4 3.65(0.45,16.10) p=0.011] at the end of Ramadan. Eight out of nine patients had increment of TSH with median increment of 2.66 mIU/L. Four out of nine patients had TSH level above the normal upper limit indicating subclinical hypothyroidism. There were no significant difference of thyroid hormones level at the end of study comparing both arm (fT3 p=0.34, fT4 p=0.66, TSH p=0.73). In terms of absolute change, there were no significant increment or reduction of all thyroid hormones level between both arms at the end of Ramadan.

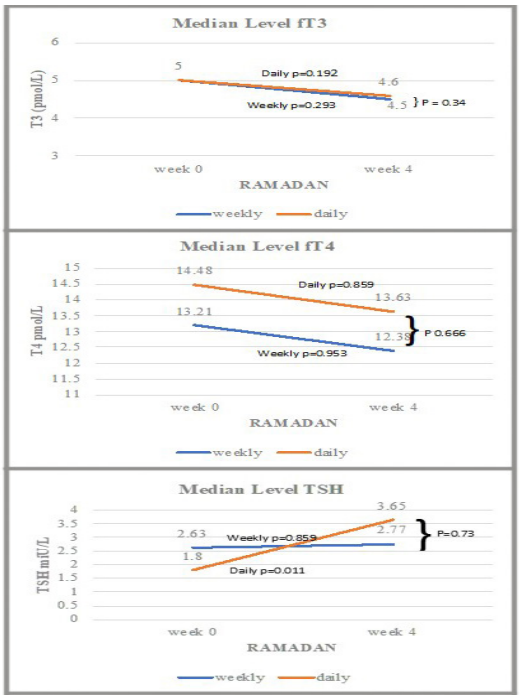

Figure 2: Median level of thyroid hormones at Week 0 and Week 4 of Ramadan

Side Effects - Thyroid Hormones after High Dose L-Thyroxine

There was a significant increment of T4 [w0 13.21(8.19,14.63) vs w2 17.43(12.38,22.55), p= 0.011] without any significant change in T3 and TSH as shown in Figure 3. Despite the significant increment in T4, patients were asymptomatic and there were no cardiac toxicities detected.

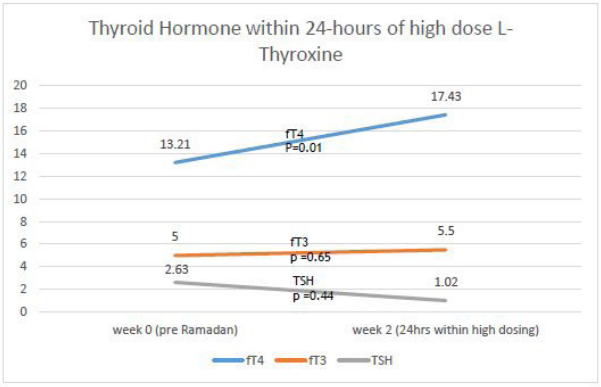

Figure 3: Median level of thyroid hormones within 24hours of high dose L-thyroxine

Side Effects -Cardiac Parameters After High Dose L-Thyroxine

The main concern of high dose L-thyroxine ingestion is cardiac toxicities. As thyroid hormones have ionotropic and chronotropic effects to the heart, arrythmia is our main concern (6). Heart rate and rhythm abnormalities were captured via electrocardiography (ECG) and 24 hrs HOLTER monitoring within 24 hrs after high dose L-thyroxine ingestion in the weekly arm.There were no tachycardia, arrythmia or significant change in the heart rate (bpm) after high dose L-thyroxine ingestion

{baseline 71(65.5,73.5)bpm vs 24hrs 69(66.5,85.5) blpm }. Clinically there were no hyperthyroid signs or symptoms reported based on wayne's clinical scoring which reflect the cardiac safety of weekly dosing.

Other Side Effects – Cognitive, Psychology ,and Lipid

In this study we assessed the cognitive function by using mini mental state examination (MMSE) and psychological function using DASS 21 scoring at baseline and at the end of study. Previous literature found that cognitive and psychological functions might be affected in hypo or hyperthyoid state (7). From our study, there were no cognitive and psychological impairment noted in both arms although daily arm showed significant increment of TSH indicating subclinical hypothyroid . Clinically patients were euthyroid throughout the study. There was no tissue hypothyroidism detected at the end of our study as reflected by no significant change in lipid parameters.

Patient's Preference

At the end of our study, patients in weekly arm who has experienced both dosing method (daily and weekly) were asked regarding their preference of L-thyroxine dosing method during Ramadan. Among all nine patients in weekly arm, three were excluded as they didn't experienced taking L-thyroxine during previous Ramadan. Among all six patients, only one patient preferred daily dosing (16.7%) as taking too many pills at a time is not tolerable . Otherwise 83.3% preferred taking weekly dosing of levothyoxine during Ramadan as it is more convenient and helps to improve medication compliance.

DISCUSSION

There are a few studies which has been looking at the efficacy and safety of weekly dosing of L-thyroxine but all of these studies were done outside Ramadan. This is a pilot randomized controlled trial which study the efficacy and safety of weekly dosing of L-thyroxine during Ramadan. As mentioned earlier, the physiological changes that occurred during prolonged regular fasting in Ramadan caused alteration in thyroid hormones thus effective replacement is important. Previous study found that during Ramadan patients become less compliance towards medication intake especially those medication with specific instruction such as thyroxine that need to be taken on empty stomach (3, 8). Since weekly dosing is a feasible option that can help to improve compliance, we investigate the efficacy and safety of weekly dosing method specifically in the month of Ramadan given the physiological changes and unique lifestyle of those who fast during this holy month.

We have conducted a randomized parallel 2 arm trial involving 18 subjects (n=9 in each arm) during Ramadan 2017 and 2018. The aim of this study is to evaluate at the efficacy and safety of weekly dosing of L-thyroxine during the month of Ramadan and to assess patient's preferance of dosing method during Ramadan. L-thyroxine should be taken on empty stomach for optimal absorption as to preserved the efficacy regardless of the timing of medication (pre-sahur or pre-bed). For weekly arm, L- Thyroxine was taken pre-sahur instead of pre-bed as the high dosage of L-Thyroxine at night may disturb their normal physiological sleep due to the high metabolic activity. As for daily arm, it is more convenient to take L-thyroxine pre-bed rather than to wake up earlier before sahur everyday. We believe that it is important that study design be practical to facilitate implementation in the real world. Although some would recommend longer than 2 hours interval between last evening meal and pre bed dosing of tyroxine, our patients took at least after 2 hours (or more) post prandial prebed dosing due to practicality in Ramadan where last meal can be as late as 10pm. The efficacy of L-thyroxine is preserved as long as it was taken at least 2 hours post prandial which has been validated by previous studies (9,10). Our study showed that weekly dosing of L-thyroxine during Ramadan is as good as daily pre-bed dosing. There were no significant change of thyroid hormones (fT3, fT4, TSH) at the end of Ramadan in those who took high dose L-thyroxine (7x daily dose) once a week. Although there was significant increment of fT4 noted in the weekly arm after high dose L-tyroxine ingestion [fT4 week 0 13.21(8.19,14.63) vs week 2 17.43(12.38,22.55) p= 0.011] there was no significant change in fT3(the active hormones). No cardiac toxicity and hyperthyroid symptoms were reported. Same findings were reported by Grebe et al, 1997 where he found that fT4 level almost tripled after high dose ingestion but changes in fT3 were slight which reflect the preferential conversion of fT4 to fT3 as a protective mechanism.

Grebe also reported mild hypothyroidism in weekly dosing and even suggested slightly larger dose of L-thyroxine for complete biochemical euthyroidism. However in our study, there were no significant thyroid hormones changes to suggest hypothyroidism in weekly arm although there were slight reduction of fT3 and fT4 with no significant increment of TSH which has also been observed in other weekly dosing studies (11, 12). Polymorphism in genes for deiodinase enzyme may be responsible for varied response to L-thyroxine treatment by different population. The common Type 2 deiodinase enzyme polymorphism has been associated with traits of impaired thyroid action at various end organ targets, hypothalamic-pituitary level and in circulating level of thyroid hormones (12, 13, 14). It is possible that these genetic differences of deiodinase enzyme might be responsible for controlled peripheral conversion of T4 to T3 resulted in maintenance of euthyroidism and avoidance of toxicity in our study.

On the contrary, we observed a significant rise of TSH at week 4 in those who took daily L-thyroxine pre-bed.

We attributed the rise of TSH level in the daily arm due to the pre bed timing of L-thyroxine as what has been observed by Karoli et al, 2013 (10). Longer digestion needed in Ramadan due to heavy meal ingestion during breaking fast. However it was not accompanied by significant reduction of fT3 or fT4 and patients were euthyroid clinically which support the efficacy and safety of pre-bed dosing.

In terms of cardiac toxicity we look at the rate and rhythm changes by monitoring the heart rate, electrocardiography (ECG) and Holter within 24 hours after high dose L-thyroxine ingestion. There were no tachycardia or cardiac arrythmia noted despite significant increment of fT4 again conforming that weekly dosing is biochemically, functionally, and clinically safe (5, 9). The significant increment of fT4 after high dose ingestion of L-thyroxine without significant increment of fT3 (active hormone) have no clinical relevance reinforcing the concept of deiodinase preferential conversion which makes weekly dosing of L-thyroxine possible and safe (16).

We also look at the cognitive and psychological functions of hypothyroid patients as ineffective L-thyroxine replacement can affect their cognitive and psychological functions (17). At the end of our study, we noted that there were no significant difference in cognitive and psychological function comparing both arms although significant anxiety was observed at baseline. Hypothyroid patients did exhibit some form of anxiety regardless of their thyroid hormones status as what reported by Sait Gonen et al, 2004 (18).

Thyroid hormones influence all major metabolic pathways. With specific regards to lipid metabolism, thyroid hormones affect synthesis, mobilization and degradation of lipids thus lipid parameters is one of tissue hypothyroidism marker (19). In our study, subclinical hypothyroid was observed in daily arm however no significant change of lipid parameters were observed at the end of our study. Lipid derangement in subclinical hypothyroidism is still debatable. Indeed, some studies reported no significant difference in lipid profile between subclinical hypothyroid patients and controls (20, 21, 22).

As one of the aim of this study is to find the feasible ways of taking L-thyroxine during Ramadan, patient's preference of dosing method were assessed at the end of study. Majority (83.3%) of them preferred to take weekly dose of L-thyroxine as it is convenient and helps to improve medication compliance especially in the month of Ramadan.

CONCLUSION

From our study we conclude that pre sahur weekly dosing of L-thyroxine is safe and as good as daily prebed dosing . It is also the most preferred dosing method during Ramadan. There are limitations that we hope to improve in future study especially in regards to the small sample size and randomization bias. Most of the previous studies on weekly L-thyroxine with larger sample size did not have thorough cardiac assessment and were using cross over design. Due to the limited resources, we proposed a multicentre study in the future in order to provide more facilities especially for cardiac asessment and to achieve higher sample size as cross-over design was not possible in our study due to the long gap between Ramadan and before crossing over. As our study only includes young patients without cardiac comorbids, the result of this study may not be generalised to all population. Despite the limitations, the results of this study are promising and it will have a great impact on the current practice of taking L-thyroxine especially during the month of Ramadan. Larger scale study is much needed in the future to support our findings.

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