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Efficacy and safety of once weekly thyroxine versus daily thyroxine as maintenance therapy of hypothyroidism: a randomised controlled clinical trial

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Abstract

Objective:

Weekly dosing of thyroxine improves compliance. We aimed to evaluate efficacy and safety of once weekly dosing of thyroxine compared to daily dosing for maintenance therapy of hypothyroidism.

Methods:

This is a parallel-group, outcome-assessment-blinded, randomised, controlled clinical trial conducted at a tertiary care hospital in Sri Lanka. Those diagnosed with primary hypothyroidism and have achieved euthyroidism with a stable dose of daily thyroxine for at least 3-months were recruited. Intervention group (IG) received seven times the regular dose once weekly. Control group (CG) received regular dose daily. Echocardiogram, blood pressure (BP), heart rate (HR) and Hyperthyroid Symptom Score (HSS) were assessed 4-6 hours after the first dose of thyroxine and at 12-weeks. Thyroid functions were assessed at 12-weeks.

Results:

Number recruited was 32 to IG(women:96.9%;mean-age:47.9±9.2years) & 24 to CG(women: 95.8%;mean-age:50.7±11.2years). Median thyroxine dose was 525mg once weekly in the IG & 75mg daily in the CG. Proportion of patients in euthyroid state at 12-weeks was not different between the groups (IG-84.4%, CG-83.3%, p = 0.57). There was no difference in the thyroid function tests at 12-weeks (mean TSH: IG-2.8µIU/mL, CG-2.1µIU/mL, p=0.348; mean free T4: IG-1.2ng/dL,CG-1.3ng/dL,p=0.445). Safety outcomes at 4-6 hours after first dose were not different between IG and CG(mean end-diastolic diameter:IG-42.1mm,CG-39.9mm,p = 0.14;mean ejection fraction: IG-60.28% ,CG-60.33% , p=0.911 ; mean systolic BP : IG-119mmHg , CG-120.8 mmHg , p=0.676; mean HR:IG-75.6bpm,CG-75.4bpm,p=0.261; mean HSS: IG - 3.5 /40, CG-4.8/40,p=0.213).IG & CG were comparable regarding safety outcomes at 12-weeks too (mean end-diastolic diameter : IG - 38.9mm , CG - 40.1mm , p = 0.643 ; mean ejection fraction: IG - 59.8% , CG-60% , p=0.429; mean systolic BP:IG-118.8mmHg,CG-116.8mmHg,p = 0.65; mean HR:IG-75.4bpm,CG-75.1bpm,p=0.919;mean HSS:IG-3.6/40,CG-4.1/40,p=0.704).

Conclusions:

Weekly dosing of thyroxine is as efficacious and safe as daily thyroxine for maintenance therapy of hypothyroidism. Further research with a larger sample size is recommended.

Keywords: Thyroxine once weekly administration; Hypothyroidism; Maintenance; Clinical trial

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Introduction

Hypothyroidism is one of the commonest endocrine disorders globally. The prevalence of hypothyroidism in the United States among those aged 12 and above is 4.6%[1]. In the United Kingdom it affects around 2% of women and 0.2% of men[2]. An epidemiological study conducted in eight cities of India, showed that one in ten of adults within the study population were hypothyroid[3]. Although prevalence rates in Sri Lanka have not been estimated, judging by the numbers of clinic attendees the numbers are quite high and only second to diabetes mellitus.

Replacement therapy with lifelong oral levothyroxine is considered the mainstay of treatment for hypothyroidism. Dose requirement can vary depending on body weight, age of the patient, pregnancy, etiology of hypothyroidism and severity of disease. The usual daily maintenance dose is 100 to 200 micrograms. Generally, the mean treatment dose is 1.6–1.8μg/kg/day but some studies have estimated the need for higher doses such as 2.0–2.1 μg/kg/day[4].

Inadequate response to thyroxine replacement is frequently encountered in clinical practice. There are multiple contributing factors, but the most encountered problem is non-compliance[4-6]. The other factors include incorrect timing of administration, malabsorption and drug interactions[4,6,7]. The absorption of thyroxine could be reduced by aluminium hydroxide, ferrous sulfate, calcium, proton pump inhibitors, oestrogen, cholestyramine and colestipol[7,8]. American Thyroid Association recommendation is to take thyroxine at least 60 minutes before breakfast and to separate thyroxine administration from other potentially interfering medications[4]. Thus, timing of therapy is crucial in the management of hypothyroidism. The patients are advised to take the drug early morning on an empty stomach, to wait for at least an hour before taking any kind of food including the bed tea, and to wait for several hours before taking the morning dose of some other medications. The need for life-long treatment on daily basis under such stringent conditions interfering with one's daily lifestyle contribute to non-compliance.

One way of addressing this issue is administering thyroxine once weekly under ideal conditions for optimal absorption. Long half-life of thyroxine makes weekly administration plausible. Thyroxine has a half-life of about 7 days and it is prolonged to 9-10 days in hypothyroid subjects[8,9]. Its biological effects may last even longer, and therapeutic actions can persist up to 3 weeks after stopping therapy[8,10].

There is some evidence from case reports, observational studies and a few small clinical trials from different countries regarding efficacy and tolerability of once weekly administration of thyroxine[11-18]. However, this treatment approach has not been well established yet and there is a need for more evidence from different populations.

This study aims to evaluate the efficacy and safety of once weekly dosing of thyroxine compared to daily dosing of thyroxine for maintenance therapy in hypothyroid patients in Sri Lanka.

Methods

Study design

This was a parallel-group, outcome-assessment-blinded, randomized controlled clinical trial conducted at a single centre in Sri Lanka. Patients fulfilling eligibility criteria were randomized in a 1:1 ratio to receive, their regular dose of thyroxine daily (control group) or seven times the regular dose of thyroxine once weekly (intervention group).

Patients

Study population consisted of patients attending the endocrinology clinic in Colombo South Teaching Hospital, Sri Lanka who were on treatment for hypothyroidism. Inclusion criteria for the trial were: age between 18 to 70 years, a diagnosis of primary hypothyroidism due to autoimmune hypothyroidism, thyroidectomy or radioiodine treatment, achieving euthyroidism with a stable dose of daily thyroxine for at least 3-months, blood pressure <140/90 mmHg, pulse rate <90 bpm, having adequate contraceptive measures for women of childbearing age and availability of meaningful consent. Exclusion criteria were: ischaemic heart disease, heart failure, cardiac arrhythmias, evidence of cardiac ischaemia on ECG or echocardiogram, ejection fraction < 50% on echocardiogram, uncontrolled hypertension (i.e BP ≥ 140/90 mmHg), renal failure with eGFR ≤ 45 ml/min/1.73m^2, chronic liver disease, liver transaminases > 5 times upper limit of normal reference range, bone fracture in previous 3 months, Paget's disease of bone, history of thyroid malignancy, malabsorption, hypoadrenalism, pregnancy, terminal illness, unavailability for follow-up and participation in another clinical trial within 3 months.

Randomization and blinding

All eligible and consenting participants were assigned to receive thyroxine once weekly or daily using simple randomization which was done centrally via telephone. Participants were assigned to interventions using a computer-generated random allocation sequence by an independent investigator who was not involved in enrolment of participants and did not have access to participant data. Participants were not blinded. Outcome assessments were done by independent assessors blinded to treatment allocation.

Interventions

Intervention group received thyroxine once weekly in a dose equal to seven times the individual's usual daily maintenance dose beginning on day 1 of the trial, with no thyroxine given on days in between. Control group continued to take their regular thyroxine dose daily. Day 1 was defined as the day immediately following the date of recruitment. Thyroxine was given to patients in both groups along with written instructions regarding its administration (frequency of administration, the specific day of the week if it is weekly thyroxine, number of tablets of thyroxine per dose, timing of administration including advise to take thyroxine on empty stomach as the first thing in the morning, not to take any food item including tea and coffee for at least an hour after taking thyroxine and not to take any other medication for four hours after taking thyroxine). A medication calendar was issued to all participants in both groups to ensure compliance. Investigators provided the thyroxine tablets to all the participants and the brand used was COX-THYROX Levothyroxine BP 50 micrograms. Trial interventions were for a period of 12 weeks. Participants received standard medical care with regard to the other management aspects based on their co-morbidities.

Trial procedure

Screening of patients started a week before recruitment. Day 0 was the recruitment day. On Day 0, patients attended the clinic after taking their regular dose of thyroxine in the morning. Details regarding demographics, thyroid status, thyroxine therapy, co-morbidities,concomitant medications, baseline blood pressure (BP) and pulse rate and rhythm were recorded. A baseline ECG was done and reported by a consultant cardiologist. Cardiologist also performed a baseline echocardiogram to look for evidence of ischaemia and heart failure and measured baseline end diastolic diameter, end systolic diameter and the ejection fraction. Self-reported patient well-being during the previous month was assessed with visual analogue Arizona Integrative Outcomes Scale (AIOS)[19]. Trial medications were handed over to the participants along with relevant advice and the medication calendar. They were advised to start the assigned trial interventions the following morning (Day 1). They were also advised to report to the investigators immediately if they develop chest pain, palpitations, syncope, shortness of breath or any other significant discomfort.

On Day 1 after taking the trial interventions in the morning, patients attended the clinic for outcome assessments due at 4-6 hours after the first dose. Outcome assessments included patient's pulse rate, BP, Hyperthyroid Symptom Score (HSS)[20], patient well-being using AIOS, electrocardiogram (ECG) and echocardiographic measurement of end diastolic diameter, end systolic diameter and ejection fraction.

Trial participants were routinely reviewed at the outpatient clinic once a month. At each monthly clinic visit participants were assessed for cardiac symptoms related to treatment with thyroxine (i.e angina, palpitations, syncope, shortness of breath), any other adverse event, HSS, medication history and compliance to trial intervention. Pulse (rate and rhythm) and BP were recorded.

At 12 weeks ± 1 week the final outcome assessment was done. Outcome assessments included patient's pulse rate, BP, HSS, patient well-being using AIOS, TSH and free T4 level, ECG and echocardiographic measurement of end diastolic diameter, end systolic diameter and ejection fraction.

Measurements

Blood pressure – BP was measured with a validated and calibrated electronic sphygmomanometer (Omron 705-IT). Patients had two readings 1-2 minutes apart and the average of the two was taken as the patient's BP.

Screening for thyrotoxicosis using HSS – HSS includes ten categories of symptoms and it is sensitive to changes in both the adrenergic and metabolic components of hyperthyroidism. A score more than 20 out of 40 is consistent with a diagnosis of thyrotoxicosis [20].

Assessment of patient well-being using AIOS - one-item visual analogue AIOS assesses self-rated

global sense of spiritual, social, mental, emotional, and physical well-being over the past 24 hours and the past month. It distinguishes relatively sicker from relatively healthier individuals [19].

Echocardiographic assessments - Transthoracic Doppler echocardiogram was performed with a dual M-mode system (Philip effinity70c- serial number 453564125971). End diastolic diameter, end systolic diameter and ejection fraction was assessed using eyeball method.

Laboratory assays for TSH and free T4 - TSH and free T4 were measured with Abbott Architect ci 8200 (TSH - reference values 0.4 -4.2 mU/L, sensitivity 0.0025mU/ml , CV <10%; fT4 - reference values 0.7 – 2.0 ng/dL, sensitivity 0.40 ng/dL, CV < 10%).

Outcomes

The primary efficacy outcome measure was the proportion of patients maintained in the euthyroid state at 12-weeks. Secondary efficacy outcomes were mean TSH and mean free T4 level at 12-weeks. The safety outcomes included mean end-diastolic diameter, mean end systolic diameter and ejection fraction on echocardiogram at 4-6 hours after the first dose of thyroxine and at 12-weeks, proportion of patients with new-onset ECG changes, mean systolic BP, mean diastolic BP, mean pulse rate, mean HSS and mean visual analogue AIOS score at 4–6 hours after first dose of thyroxine and at 12-weeks.

Statistical analysis

The planned sample size was 100 which was a feasible number in the given setting. However, only 56 could be recruited as COVID-19 interfered with recruitment and follow up of patients. Intention-to-treat analysis was done for all the outcomes except echocardiographic findings at 12-weeks. Per protocol analysis was done for end diastolic diameter, end systolic diameter and ejection fraction at 12-weeks. The null hypothesis regarding the outcomes was that they were not different between the patients receiving thyroxine daily and once weekly. Chi-square test was used to compare categorical data and independent sample t test was used to compare numerical data. Fisher's exact test

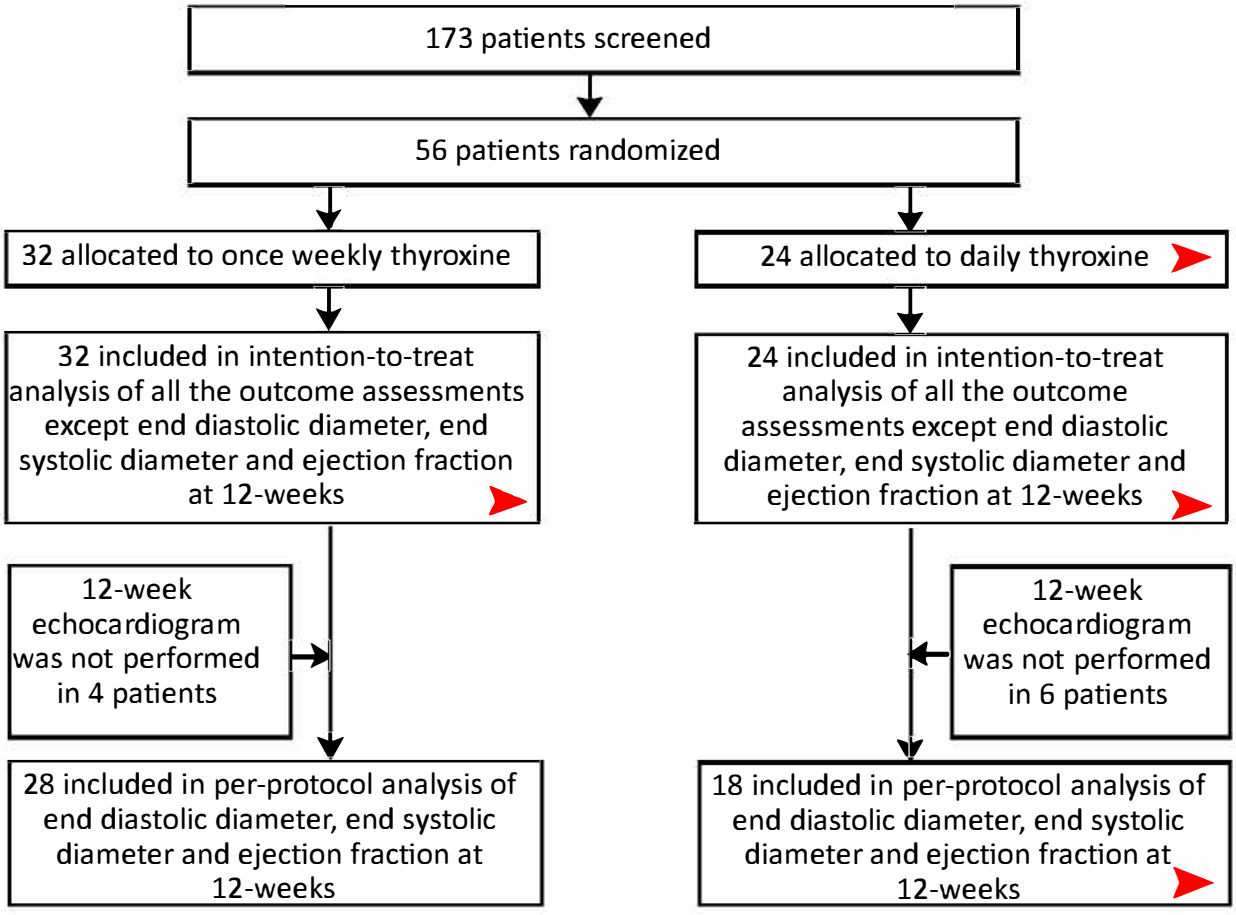

Figure 1: Study profile.

was used to compare categorical data when expected sample size in any cell was <5. Standard deviation was calculated for all means. Odds ratio with 95% confidence intervals were calculated for categorical data and mean difference with 95% confidence intervals was calculated for numerical data. Statistical significance was checked at 5% significance level. Data analysis was performed using SPSS (V.21.0)

Ethics

Written informed consent was obtained from all participants prior to recruitment. The ethical approval for the trial was obtained from Ethics Review Committee of the Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka (Reference number: 67/17). The trial is registered with Sri Lanka Clinical Trials Registry (Registration number: SLCTR/2018/007).

Results

From July 2018 to March 2020, 56 patients were randomized. 32 patients were assigned to once weekly thyroxine group and 24 were assigned to daily thyroxine group. All randomized patients completed Day 1 outcome assessments and 12-week outcome assessments except echocardiography. 12-week echocardiographic assessments were done in 46 patients. (Figure 1).

The mean age of the overall population was 49.1±10.1 years and 96.4% were women. There was no statistically significant difference in the baseline characteristics of the two treatment groups (Table 1). After randomization the median thyroxine dose received by the intervention group (IG) was 525 µg (range 175 – 1050 µg) once weekly. The median dose of the control group(CG) was 75 µg (range 25 – 150 µg) daily. Compliance to treatment was 100% in both groups.

The two groups were not significantly different with regard to the thyroid status at 12-weeks (Table 2).

Proportion of participants who were euthyroid at 12-weeks was 84.4% in the once weekly thyroxine group and 83.3% in the daily thyroxine group (OR=1.08,95% CI0.26-4.54;p=0.916)(Table 3). Mean TSH and free T4 levels at 12-weeks were comparable in the two groups (Table 3). There was no significant difference between the intervention group and the control group regarding pulse, BP, echocardiographic measurements, HSS and patient well-being (measured with AIOS) at 4-6 hours after the first dose of thyroxine as well as at 12-weeks. (Table 3).

Table 1 : Baseline characteristics (n=56)

	Once weekly thyroxine (n=32)	Daily thyroxine (n=24)	p
Age, years, mean (SD)	47.9 (9.2)	50.7 (11.2)	0.313
Women, n (%)	31 (96.9)	23 (95.8)	0.835
Autoimmune hypothyroidism, n (%)	30 (93.8)	22 (91.7)	0.484
Regular daily thyroxine dose prior to randomisation, µg, mean (SD)	78.9 (31.2)	69.8 (31.3)	0.284
Systolic BP, mmHg, mean (SD)	118.9 (14.2)	122 (16)	0.446
Diastolic BP, mmHg, mean (SD)	75.4 (9.8)	76.4 (9.9)	0.709
Pulse rate, bpm, mean (SD)	73.4 (10.4)	73.8 (12)	0.898
TSH, µIU/mL, mean (SD)	2..2 (1.2)	2.2 (1.4)	0.870
Free T4, ng/dL, mean (SD)	1.4 (0.6)	1.3 (0.3)	0.439
End-diastolic diameter, mm, mean (SD)	41.6 (5.2)	41.5 (6.5)	0.973
End-systolic diameter, mm, mean (SD)	24.3 (4.7)	26.6 (4.7)	0.069
Ejection fraction, %, mean (SD)	60.6 (2.2)	60.1 (1.1)	0.382
AIOS (out of 10), mean (SD)	7.8 (1.8)	8 (1.7)	0.661

BP=blood pressure; TSH=thyroid stimulating hormone; T4=thyroxine; AIOS= Arizona Integrative Outcomes Scale

Table 2 : Thyroid status at 12-weeks

	Once weekly thyroxine (n=32)	Daily thyroxine (n=24)	p
Euthyroid, n (%)	27 (84.4)	20 (83.3)	0.916
Hypothyroid, n (%)	3 (9.4)	1 (4.2)	0.627
Hyperthyroid, n (%)	2 (6.3)	3 (12.5)	0.642

There was no difference between the two groups with regard to BP, pulse rate and HSS measured at 4-weeks (SBP: IG – 119.2 mmHg, CG – 119.4 mmHg, p = 0.949; DBP: IG – 74.7 mmHg, CG – 74.1 mmHg, p = 0.799; pulse rate: IG – 73.6 bpm, CG – 74 bpm, p = 0.859; HSS: IG - 3.9/40, CG – 4.8/40, p = 0.545) and 8-weeks (SBP: IG – 118.2 mmHg, CG – 123.6 mmHg, p = 0.193; DBP: IG – 75.7 mmHg, CG – 75.3 mmHg, p = 0.844; pulse rate: IG – 76.1 bpm, CG – 75.3 bpm, p = 0.741; HSS: IG - 3.3/40, CG – 4.2/40, p = 0.5). There were no new onset ECG changes, tachyarrhythmias, stable angina, acute coronary syndromes, heart failure or deaths in any trial participant during the intervention period of 12 weeks. No Serious Adverse Events (SAEs) occurred.

Among the 32 patients who were in the once weekly thyroxine group 19 (59.4%) preferred once weekly administration over daily administration.

Discussion

In this controlled clinical trial, we found that once weekly administration of thyroxine is as efficacious and as safe as daily administration of thyroxine for maintenance of euthyroidism in hypothyroid patients. To date there is only limited evidence to support this approach and there are no previous studies among Sri Lankan patients. Strengths of our study include having a reasonable sample size compared to the previous clinical trials and assessing efficacy as well as acute and chronic toxicity with regard to hyperthyroidism, echocardiographic parameters, ECG changes, BP and pulse rate. We also assessed patient wellbeing with AIOS.

We found that the proportion of patients who were maintained euthyroid at the end of the follow up period was not significantly different between the two groups receiving thyroxine daily and once weekly. This is evidence to indicate that once weekly administration of thyroxine in a dose equal to seven times the regular thyroxine dose is as efficacious as daily administration.

However, in a previous trial conducted by Grebe et al comparing daily dosing of thyroxine versus once weekly dosing with seven times the daily dose, thyroid function tests demonstrated mild hypothyroidism towards the end of the week following treatment with weekly thyroxine[16]. This indicated that for complete biochemical euthyroidism a dose larger than 7 times the normal daily dose might be required. Rajput et al also conducted a randomized crossover trial to compare the effect of daily versus weekly thyroxine in 100 hypothyroid patients who were biochemically euthyroid on stable doses of thyroxine for at least 3 months before recruitment[17]. They found that the thyroid function tests remained within normal range at 6-weeks, but the TSH level was significantly higher and T3 and T4 levels were significantly lower with weekly administration of thyroxine. In our study the mean serum TSH and mean free T4 were within normal range in both groups with no significant difference between them. We observed that by the end of the follow up period of 12-weeks, three patients in the once weekly treatment group and one patient in the daily treatment group were biochemically hypothyroid. Even though there is a trend towards development of hypothyroidism with once weekly treatment The difference was not statistically significant. On the other hand, there were a few patients who were biochemically hyperthyroid by the end of the follow up period. It was seen in two patients who received thyroxine once weekly and three patients who received thyroxine daily. Wasoori et al from India, conducted an observational study to evaluate once weekly administration of thyroxine in 180 adult patients with hypothyroidism and has reported that one patient developed hyperthyroid symptoms during the study period[14].

With administration of seven times the regular daily dose, an acute rise in serum T4 and T3 levels is expected. In the randomized crossover trial conducted by Grebe et al in 12 hypothyroid patients, the mean peak free T4 and peak free T3 were significantly higher in those who received thyroxine weekly compared to those who received thyroxine daily[16].

Table 3 : Efficacy and safety outcomes at 4-6 hours after the first dose of thyroxine and at 12-weeks

	Once weekly thyroxine (n=32)	Daily thyroxine (n=24)	OR (95% CI)	Mean difference (95% CI)	p
Efficacy Outcomes					
Proportion of patients euthyroid at 12 weeks, n (%)	27 (84.4)	20 (83.3)	1.08 (0.26-4.54)	-	0.916
TSH at 12 weeks, μIU/mL, mean (SD)	2.84 (3.72)	2.08 (1.36)	-	0.76 (-0.85 to 2.36)	0.348
Free T4 at 12 weeks, ng/dL, mean (SD)	1.19 (0.36)	1.27 (0.41)	-	-0.08 (-0.2 to 0.13)	0.445
Safety Outcomes at 4-6 hours after the first dose of thyroxine					
End-diastolic diameter, mm, mean (SD)	42.1 (3.9)	39.9 (6.8)	-	2.15 (-0.73 to 5.02)	0.14
End-systolic diameter, mm, mean (SD)	24.06 (3.58)	28.04 (6.24)	-	-3.98 (-6.63 to -1.33)	0.052
Ejection fraction, %, mean (SD)	60.28 (1.78)	60.33 (1.63)	-	-0.05 (-0.98 to 0.88)	0.911
Systolic BP, mmHg, mean (SD)	118.98 (14.4)	120.79 (17.8)	-	-1.81 (-10.44 to 6.82)	0.676
Diastolic BP, mmHg, mean (SD)	78.33 (9.41)	75.92 (11.15)	-	2.41 (-3.11 to 7.93)	0.385
Pulse rate, bpm, mean (SD)	72.56 (8.24)	75.42 (10.56)	-	-2.85 (-7.89 to 2.18)	0.261
Hyperthyroid Symptom Score (out of 40), mean (SD)	3.5 (3.08)	4.75 (4.34)	-	-1.25 (-3.24 to 0.74)	0.213
Visual analogue AIOS (out of 10), mean (SD)	8.13 (1.68)	7.17 (2.01)	-	0.96 (-0.03 to 1.95)	0.058
Safety Outcomes at 12 weeks					
End-diastolic diameter, mm, mean (SD)[a]	38.9 (8.53)	40.11 (8.62)	-	-1.21 (-6.42 to 4.01)	0.643
End-systolic diameter, mm, mean (SD) [a]	28.62 (7.89)	27.78 (5.96)	-	0.84 (-3.55 to 5.23)	0.702
Ejection fraction, %, mean (SD) [a]	59.82 (0.95)	60 (0)	-	-0.18 (-0.63 to 0.27)	0.429
Systolic BP, mmHg, mean (SD)	118.78 (18.22)	116.83 (11.7)	-	1.95 (-6.59 to 10.49)	0.65
Diastolic BP, mmHg, mean (SD)	82.67 (33.25)	74.67 (6.78)	-	8 (-5.84 to 21.85)	0.252

Pulse rate, bpm, mean (SD)	75.41 (8.99)	75.13 (11.5)	-	0.28 (-5.21 to 5.77)	0.919
Hyperthyroid Symptom Score (out of 40), mean (SD)	3.63 (3.48)	4.08 (5.47)	-	-0.46 (-2.86 to 1.94)	0.704
Visual analogue AIOS (out of 10), mean (SD)	7.94 (1.78)	7.88 (1.33)	-	0.06 (-0.81 to 0.93)	0.886

TSH=thyroid stimulating hormone; T4=thyroxine; BP=blood pressure; AIOS= Arizona Integrative Outcomes Scale

[a]once weekly thyroxine, n=28; daily thyroxine, n=18

A similar finding has been reported by Bornschein et al too[17]. This acute rise in thyroid hormones could result in development of thyrotoxic symptoms and cardiovascular effects such as increased blood pressure, pulse rate and echocardiographic changes. However, in our study none of the patients developed hyperthyroid symptoms after the first dose of thyroxine. The HSS score was comparable in the two groups. There was no difference between the two groups with regard to echocardiographic findings that included end diastolic diameter, end systolic diameter and the ejection fraction. No difference was found in systolic and diastolic blood pressure or pulse rate. There were no ECG changes in any trial participant. We also looked at the chronic effects of recurrent exposure to higher levels of thyroid hormones and did not find any difference in weekly administration compared to daily administration regarding echocardiographic assessments, ECG findings, blood pressure or pulse at 12 weeks of treatment. There are two small crossover clinical trials previously conducted by Grebe et al (n = 12) and Bornschein A et al (n = 14) which evaluated cardiac effects of once weekly administration of thyroxine compared to daily administration[16,18]. They also have reported that there was no difference in echocardiographic parameters acutely or chronically. However, none of the previous studies reported on ECG findings, blood pressure or pulse rate.

Patient well-being is another important parameter when we consider changing treatment regimens. In our trial visual analogue AIOS score for assessing patient well-being was not significantly different between the two groups acutely after the first dose or long term at 12-weeks of treatment. However, in the trial conducted by Rajput et al there was improvement in quality of life with weekly treatment compared to daily treatment[17].

The main limitation of our trial is the small sample size. However up to now there had been only one clinical trial with a sample size larger than ours[17]. We believe that our trial adds to the existing limited evidence to the subject of intermittent administration of thyroxine as an option for treatment of hypothyroidism. Another limitation was that we have measured thyroid function tests only at the end of the intervention period. Therefore, we were unable to capture the possible fluctuations in thyroid function tests in between. We did the Hyperthyroid Symptom Score after the first dose to screen for hyperthyroidism induced by acute rise in T4 level following once weekly dosing. However, it would have been ideal if we did the thyroid functions tests. There is a possibility of thyroxine level becoming too low towards the end of the week in those who received once weekly thyroxine. This possible change was also not captured as thyroid function tests were not done at that point.

Conclusions

Weekly dosing of thyroxine with a dose equal to seven times the regular daily dose is an efficacious and safe alternative to daily thyroxine for maintenance therapy of hypothyroidism. This approach is likely to be particularly useful for patients with compliance issues. Further research with a larger sample size is recommended.

Funding

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Conflict of Interest

None declared.

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