Comparing the Clinical Effectiveness of Levothyroxine Intake before Breakfast versus at Bedtime in Patients with Hypothyroidism

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Abstract

Introduction: Levothyroxine is the treatment of choice for hypothyroidism. Several studies have explored Levothyroxine administration at bedtime as an alternative dosing regime to the traditional morning regime and reported improvements in thyroid functions.

Objective: This study aimed to compare the clinical effectiveness of Levothyroxine administration, either in the morning or at bedtime, on the serum thyroid stimulating hormone (TSH) and thyroxine (T4) levels as well as to determine the effect of Levothyroxine administration time on patients' quality of life (QoL).

Method: A quasi interventional study was conducted at the Endocrinology Clinic of Tuanku Ja'afar Seremban Hospital from July to October 2017. Recruited hypothyroid patients were allocated to either before breakfast or at bedtime Levothyroxine regime. The primary outcomes measured were the changes in TSH and T4 levels and the patients' QoL was assessed using the 36-Item Short Form Survey (SF-36) instrument. The outcomes were measured before the beginning of the study and after 12 weeks.

Results: Thirty-five patients completed the 12-week study period. The serum TSH and T4 level showed improvement in the bedtime regime group, in which the mean TSH level reduced from 2.5mIU/L (standard deviation (SD) 1.3mIU/L) to 1.8mIU/L (SD 1.0mIU/L) (p=0.13) while the mean T4 level increased from 15.3pmol/L (SD 2.7pmol/L) to 15.7pmol/L (SD 3.3pmol/L) (p=0.51). However, these differences were not statistically significant when compared with the morning regime group. Patients in both regimes reported statistically significant improvements in three SF-36 QoL parameters after twelve weeks namely role limitations due to physical problems, social functioning and pain. The QoL scores differences between the two groups after twelve weeks, however, were not statistically significant.

Conclusion: Our study showed that administration of Levothyroxine at bedtime could be an alternative dosing regime to the traditional morning regime which could potentially improve patients' thyroid profiles and QoL.

Keywords: Levothyroxine, hypothyroidism, before breakfast, at bedtime

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Introduction

Thyroid hormones, iodine-containing thyroxine (T4) and triiodothyroxine (T3) are regulated by the hypothalamic–pituitary–thyroid gland (HPT) axis through a negative feedback mechanism (1,2). Low concentrations of serum T4 and T3 hormones triggers the release of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid stimulating hormone (TSH) from the pituitary gland (3). TSH then stimulates the thyroid follicular cells on the thyroid gland to synthesis T4 and T3 and increases their concentration in the bloodstream. An increase in serum concentrations signals the inhibition of TRH and TSH release via the negative feedback mechanism (4).

The predominant hormone produced by the thyroid gland is T4 and only approximately 20% of the hormones produced are T3 which is the hormone required by the body. The production of the T3 hormone by the thyroid gland is insufficient to meet the daily requirements of the body and therefore, the remaining 80% is obtained from the peripheral conversion of T4 to T3 by enzyme deiodinase. The metabolically active T3 hormone has a 10-fold greater affinity for thyroid receptors in the organs and is responsible in mediating the physiological functions of thyroid hormone in the body (5).

Hypothyroidism is a common endocrine disorder in which the body lacks sufficient thyroid hormone. The prevalence of hypothyroidism increases with age, with more than 10% of the women of over 60 years having subclinical hypothyroidism (6). There can be many factors contributing to hypothyroidism namely autoimmune disease such as Hashimoto's thyroiditis, surgical removal of the thyroid, radiation treatment, other medications and either too much or too little iodine which is necessary for the production of thyroid hormone. Regardless of the factors contributing to the condition, Levothyroxine is the first line treatment for hypothyroidism (7).

However, the oral intake of Levothyroxine should follow a few restrictions to ensure the optimal therapeutic efficacy of the drug. Levothyroxine absorption is the lowest when taken with food (8). Therefore, patients are advised to take the drug before breakfast. However, in reality patients wait a varying length of time before eating food and this may have an effect on compliance. Besides that, the consumption of coffee when the day begins may also influence Levothyroxine absorption. Levothyroxine is also known to interact with other medications such as cholestyramine resin, sucralphate, iron sulphate, calcium preparations, aluminium antacids, raloxifene, activated charcoal, various soya products, as well as food and herbal remedies (9).

Several studies have explored Levothyroxine administration at bedtime as an alternative dosing regime to the traditional morning regime and had reported marked improvements in the thyroid functions (10-12). Therefore, the aims of this study were to compare the clinical effectiveness of Levothyroxine administration taken in the morning or at bedtime on the serum TSH and T4 levels, and to determine the effect of different administration time of Levothyroxine on patients' quality of life (QoL).

Method

Study Design and Setting

A quasi, interventional study was conducted in a state hospital, Tuanku Ja'afar Seremban Hospital (HTJS) in Malaysia. This study was conducted in the Endocrinology Clinic from July 2017 to October 2017. The study protocol was reviewed and approved by the Ministry of Health Malaysia Medical Research Ethics Committee (MREC) and was registered in National Medical Research Register (NMRR).

Clinical effectiveness was defined as the improvement in thyroid hormones levels (TSH and T4). Patients were divided into two groups representing the morning and bedtime regime. Patients in the morning regime was required to take their dose of Levothyroxine at 8.30am and patients in the bedtime regime was required to take their dose of Levothyroxine at 10pm. For patients who find it hard to adjust their lifestyle to the suggested timing, they were advised to consume Levothyroxine 30 minutes before breakfast and 1 hour before retiring to bed according to the regime they are assigned too.

The primary outcomes measured were the changes in thyroid hormone levels (TSH and T4) while the secondary outcomes measured were QoL, serum creatinine, liver function, body mass index (BMI), heart rate and blood pressure. Patient's quality of life was assessed using the 36-Item Short Form Survey Instrument (SF-36). Patient's baseline thyroid profiles (TSH and T4 level) and patients' quality of life were taken prior to the start of the study and after 12 weeks. The data collected was analysed using the Statistical Package for the Social Sciences (SPSS). Multiple paired t-test was used to demonstrate the differences between the study groups.

Patient Recruitment

All patients age 18 and above who were diagnosed with primary hypothyroidism of any cause, are consistent with their follow ups at the clinic, able to swallow tablets without any difficulty and consistent on the same dose of Levothyroxine for 6 months before study enrolment were recruited.

Pregnant woman and lactating mother were excluded. Patients who were taking the following drugs concomitantly, such as oestrogen / progesterone replacement therapy, oral contraceptives, testosterone replacement, or tamoxifen within the last 3 months, bile acid sequestrants, aluminium hydroxide antacids, sodium polystyrene sulfonate, cholestyramine, colestipol, raloxifene, high-fibre diets, and diets high in soy were excluded. Patients on medications that may potentially affect the serum TSH concentrations, such as steroids, T3 preparations, dopamine analogues, or somatostatin analogues, and taking medications affecting thyroid hormone metabolism such as phenytoin, carbamazepine, sertraline, and rifampicin were also excluded.

Patient's Compliance

To ensure the patients' compliance, each patient was supplemented with a copy of patient diary where the patient was required to record the time of Levothyroxine consumptions throughout the study period. This served as a mean to identify whether the patients had consumed their Levothyroxine medication in the correct way. The importance of self-reporting about their adherence was explained to the patients. The recruited patients were also required to bring along their refill prescriptions for Levothyroxine to ensure that they had refilled their prescriptions according to the To Come Again (TCA) appointment note from the pharmacy.

Results

A total of 35 patients fulfilled the inclusion and exclusion criteria in this study and completed the 12-week study period. The gender ratio of male to female was 1:10 in the morning group and 1:1.6 in the bedtime group. The Shapiro-Wilk Test showed that the age of patients was normally distributed (p=0.244). The patients' age had a range of 52 years between 18 and 70 years old in the morning group while the bedtime group had a range of 56 years between 19 and 75 years old. Malay was the most common ethnic group in this study followed by Indian and Chinese. However, there were no Chinese patients in the bedtime group.

Table 1: Demographics and baseline characteristics of the study population (N=35)

Characteristics	Morning Group (n=22)	Bedtime Group (n=13)
Gender, n		
Male	2	5
Female	20	8
Age, mean (SD), year	43.7 (14.2)	49.0 (19.5)
Elderly status, n		
Elderly (> 60)	3	4
Non-elderly (18-60)	19	9
Race, n		
Malay	10	9
Chinese	4	0
Indian	8	4
BMI, kg/m^2, mean (SD)	23.6 (4.2)	26.7 (5.3)
Weight Classification, n		
Underweight	7	2
Normal	1	4
Overweight	5	2
Pre-obese	6	4
Obese	3	1
Cigarette-smoking status, n		
Yes	0	3
No	21	10
Ex-smoker	1	0
Alcohol status, n		
Yes	0	0
No	22	13
Aetiology of hypothyroidism, n		
Hashimoto disease	0	2
Post-radioactive Iodine 131	5	6
Thyroidectomy	10	
Others	7	0
Patients who used other medications		
Yes	15	8
No	7	5
Duration of hypothyroidism, year, median (IQR)	4.5 (5.0)	5.0 (5.0)
Levothyroxine dosage, µg, median (IQR)	75 (56)	75 (50)
TSH level, mIU/L, mean (SD)	1.6 (1.1)	2.5 (1.3)
Free thyroxine, T4 level, pmol/L, mean (SD)	15.8 (3.7)	15.2 (2.6)

Abbreviation: BMI – body mass index; SD – standard deviation; IQR – interquartile range

The mean BMI for morning group was in the overweight category while the bedtime group was in the obese category. Most of the patients in both groups did not smoke and none of them drank alcohol. In the morning group, the mode aetiology of hypothyroidism was thyroidectomy while bedtime group was post-radioactive Iodine 131. Other aetiology includes unspecified hypothyroidism, autoimmune hypothyroidism, congenital hypothyroidism, postpartum hypothyroidism, primary hypothyroidism, subclinical hypothyroidism and thyroid lymphoma. The median duration of hypothyroidism and Levothyroxine dosage were not much different between the two groups. Concurrent medications were taken by 15 patients from the morning group and eight patients from the bedtime group. Among these 23 patients, nine patients took calcium supplement, two patients took iron supplement, 10 patients with vitamins supplement and 18 patients had other medications such as Amlodipine, Simvastatin, Metformin, Cardiprin, Gliclazide, Metoprolol, Bisoprolol, Perindopril, Omeprazole and Magnesium Trisilicate Mixture (MMT). Note that one patient might take more than one concurrent medication. The characteristics of patients at baseline were shown in Table 1.

The results of the primary and secondary outcomes were tabulated in Table 2 and Table 3 while the results on quality of life were summarised in Table 4. It was reported that at the end of 12 weeks, the bedtime regime showed a reduction in mean TSH level from 2.5mIU/L (SD 1.3mIU/L) to 1.8mIU/L (SD 1.0mIU/L) in comparison to the morning regime which showed an increase in TSH level, from 1.6mIU/L (SD 1.1mIU/L) to 2.0mIU/L (SD 1.4mIU/L). However, these changes were not statistically significant. The mean T4 level was reported to have a slight increase in the bedtime group from 15.3pmol/L (SD 2.7pmol/L) to 15.7pmol/L (SD 3.3pmol/L). In contrast, the morning group showed slight reduction from 15.8pmol/L (SD 3.73pmol/L) to 15.6pmol/L (SD 3.0pmol/L). Nevertheless, this was also not statistically significant. When comparing between the morning and bedtime group at the end of 12 weeks, it was found that there was no significant difference in the means of both TSH and T4 levels.

Secondary outcomes showed significant difference between means of the two groups in serum creatinine level (p=0.02) and BMI (p=0.04). There were no significant differences between the two study groups in term of albumin level, ALP level, ALT level and vital signs.

In referring to Table 4, the QoL assessment using the SF-36 instrument demonstrated an improvement of all parameters in the bedtime regime as compared to baseline except for general health. On the other hand, the morning regime group showed improvements in only a few parameters such as limitations due to physical and emotional problems, energy levels, pain and overall general health as compared to the baseline. There was no statistically significant difference between the two groups in terms of QoL scores.

Table 2: Comparison of biochemical parameters of the morning and bedtime groups at baseline and at the end of 12 weeks (N=35)

Biochemical parameters	Mean (SD)				Mean Difference (95% CI)		p value [a]	
	Morning Group		Bedtime Group		Morning	Bedtime	Morning	Bedtime
	Baseline	12 weeks	Baseline	12 weeks	Group	Group	Group	Group
TSH level, mIU/L	1.6 (1.1)	2.0 (1.4)	2.5 (1.3)	1.8 (1.0)	-0.4 (-1.0, 0.2)	0.7 (-0.2, 1.6)	0.158	0.129
T4 level, pmol/L	15.8 (3.7)	15.6 (3.0)	15.2 (2.6)	15.7 (3.3)	0.2 (-1.5, 1.9)	-0.5 (-2.0, 1.1)	0.817	0.505
Creatinine, µmol/L	77.5 (27.4)	72.2 (16.7)	108.7 (30.5)	98.0 (30.9)	5.3 (-9.4, 20.1)	10.7 (-3.5, 24.9)	0.444	0.114
Albumin	39.2 (3.7)	40.5 (4.8)	37.2 (2.0)	42.5 (2.7)	-1.2 (-4.3, 1.8)	-5.3 (-8.2, -2.5)	0.396	**0.005**
ALP	68.3 (13.5)	67.8 (15.7)	81.3 (15.6)	88.7 (13.0)	0.6 (-5.3, 6.4)	-7.3 (-12.9, -1.8)	0.830	**0.019**
ALT	22.0 (8.9)	22.3 (10.0)	73.8 (69.5)	44.8 (43.1)	-0.3 (-5.0, 4.5)	29 (-1.5, 59.5)	0.909	0.058
BMI, kg/m2	23.6 (4.2)	23.2 (3.8)	26.7 (5.3)	26.6 (5.2)	0.3 (-0.1, 0.8)	0.1 (-0.3, 0.6)	0.155	0.543
Heart rate, beats/min	84.7 (12.3)	85.8 (11.2)	81.0 (18.8)	80.2 (15.5)	-1.0 (-8.8, 6.7)	0.8 (-5.6, 7.1)	0.781	0.796
SBP, mmHg	122.0 (18.0)	126.2 (21.4)	124.9 (21.6)	126.6 (17.1)	-4.3 (10.5, 2.0)	-1.7 (-10.7, 7.4)	0.169	0.691
DBP, mmHg	74.9 (8.5)	77.3 (8.0)	72.0 (8.9)	74.2 (9.0)	-2.5 (-4.8, -0.1)	-2.2 (-5.4, 1.1)	0.042	0.175

[a] Multiple paired t-test

Abbreviation: CI – confidence interval, SD – standard deviation

Table 3: Comparison of biochemical parameters of the morning and bedtime groups at the end of 12 weeks (N=35)

Biochemical Parameters	Mean (SD)		Mean Difference (95% CI)	p value [a]
	Morning Group	Bedtime Group		
TSH level, mIU/L	2.0 (1.4)	1.8 (1.0)	0.2 (-0.7, 1.1)	0.606
T4 level, pmol/L	15.6 (3.0)	15.7 (3.3)	-0.2 (-2.4, 2.0)	0.884
Creatinine, µmol/L	66.0 (17.9)	92.0 (33.2)	-26.0 (-46.5, -5.5)	**0.015**
Albumin	40.7 (4.4)	40.2 (4.8)	0.4 (-3.6, 4.5)	0.826
ALP	72.3 (26.7)	87.3 (12.4)	-15.0 (-37.2, 7.1)	0.172
ALT	21.3 (9.5)	42.6 (40.8)	-21.3 (-58.1, 15.6)	0.210
BMI, kg/m2	23.2 (3.8)	26.6 (5.2)	-3.3 (-6.4, -0.2)	**0.036**
Heart rate, beats/min	85.8 (11.2)	80.2 (15.5)	5.5 (-3.7, 14.8)	0.229
SBP, mmHg	126.2 (21.4)	126.6 (17.1)	-0.4 (-14.6, 13.8)	0.956
DBP, mmHg	77.3 (8.0)	74.2 (9.0)	3.1 (-2.8, 9.1)	0.289

[a] Multiple paired t-test

Abbreviation: CI – confidence interval, SD – standard deviation

Table 4: SF-36 QoL scores, expressed as mean (SD), of the morning and bedtime groups at the end of 12 weeks

SF-36 Item	Morning Group		Bedtime Group		p value [a]
	Baseline	12 weeks	Baseline	12 weeks	
Physical functioning	83.86 (11.54)	82.05 (9.84) (p=0.42)	81.54 (15.33)	85.00 (5.40) (p=0.51)	p=0.33
Role limitations due to physical problems	46.36 (34.58)	66.39 (22.77) **(p=0.04)**	51.92 (27.88)	75.00 (22.82) **(p=0.03)**	p=0.29
Role limitations due to emotional problems	53.25 (45.52)	71.75 (30.37) (p=0.11)	51.27 (35.01)	69.25 (21.36) (p=0.15)	p=0.80
Vitality	64.46 (15.75)	73.18 (8.10) **(p=0.02)**	72.31 (10.33)	73.46 (10.49) (p=0.75)	p=0.93
Mental health	82.00 (7.38)	79.36 (5.29) (p=0.16)	78.15 (5.32)	79.08 (7.15) (p=0.71)	p=0.89
Social functioning	80.68 (11.40)	73.77 (7.78) **(p=0.02)**	69.23 (10.96)	77.89 (12.70) **(p=0.10)**	p=0.24
Pain	68.75 (8.99)	76.82 (9.13) **(p=0.01)**	67.89 (11.13)	78.65 (7.75) **(p=0.01)**	p=0.55
General health	83.09 (10.45)	85.91 (10.76) (p=0.28)	80.15 (12.82)	79.58 (10.33) (p=0.61)	p=0.11

[a] Multiple paired t-test, showing the difference between the morning and bedtime groups at the end of 12 weeks.

Discussion

The findings of our study were consistent with that of Bolk *et al*. (2007) and Bolk *et al*. (2010) which suggested that the bedtime regime is superior at improving thyroid profiles compared to the morning regime, although our results were not statistically significant. A possible explanation for improvement of thyroid profiles in the bedtime group may be due to better absorption of Levothyroxine in the gut in the fasted state. Bolk *et al*. (2010) stated that 30 minutes before breakfast may not be sufficient to promote complete absorption of Levothyroxine in contrast to patient who take their medication 2 hours or later after dinner. A longer fasting state may have increased the bioavailability of the drug. Besides, higher secretion of gut gastric acid at night as opposed to morning may provide a feasible environment for the optimal absorption of Levothyroxine (10,11). Rajput *et al*. also mentioned that slower gastric motility at night contributed to increased bioavailability of the drug for

absorption and a reduction in the activity of deiodinase enzyme might change the pharmacokinetics of the drug (12).

Based on the results of our study, clinicians could inform patients with hypothyroidism that Levothyroxine intake at bedtime is a good alternative to the morning intake, as long as the Levothyroxine is taken on empty stomach. For patients who do not attain normal thyrotropin or free T4 levels with morning Levothyroxine intake, a switch to the bedtime regime can be recommended. Drug information resources and guidelines on the management of hypothyroidism require revisions in this respect (11).

Our study demonstrated that patients in both the morning and bedtime regimes reported statistically significant improvements in some of the SF-36 QoL parameters after twelve weeks of treatment including role limitations due to physical problems, social functioning and pain. The differences between the two groups in terms of QoL scores after twelve weeks, however, were not statistically significant. A similar finding was found by Samuels *et al*. (2018) who reported that changing the doses of Levothyroxine to alter TSH levels to low-normal, high-normal, or mildly elevated range did not affect the QoL of hypothyroid patients. Also, the authors noted that most published studies could not demonstrate significant changes in the QoL of subclinical hypothyroid subjects (13). Similarly, Tan *et al*. (2019) reported that the QoL of patients on Levothyroxine therapy for hypothyroidism was not associated with their clinical parameters and thyroid hormones levels, but poorer QoL was significantly associated with their co-morbidities and symptoms of hypothyroidism (14).

The available literature discussing the change in administration times in comparison to the efficacy of Levothyroxine mostly reported a study period of maximum of 12 weeks, which may not be sufficient to conclude if the change achieved in thyroid profiles is significant. Longer duration of study period should be conducted to identify the long-term effects. The lack of data available regarding the pharmacokinetics, the maximum serum concentration and the area under the concentration curve for thyroid hormones also makes it difficult to conclude if the night regime is an equivalent alternative dosing choice. An hourly serum concentration at time 0, 1, 2, 3, 6, 9, 12, 24 of Levothyroxine ingestion would probably mirror the change in thyroid profiles better rather than a cumulative concentration after 12 weeks (15). The lack of this information in the available literature makes it difficult to determine the exact mechanism of action of nocturnal efficacy of Levothyroxine. However, this process would incur an increase in cost, which may be difficult to fund.

Conclusion

Although not statistically significant, the results of our study showed that the bedtime regime of Levothyroxine is slightly better compared to the morning regime in terms of improving the thyroid profiles as well as in the quality of life of the patients. Future work is necessary to address the shortcomings of our research and to strengthen the findings. Nevertheless, in our opinion, prescribers and pharmacists should inform and educate patients on the availability of this alternative and possibly superior dosing regimen for Levothyroxine in hypothyroidism, particularly for patients whom are not responding well to the morning regime and those that find the bedtime regime a more convenient alternative befitting their daily schedules.

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Conflict of Interest Statement

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