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Original Research Article

Comparing the effects of alternate day and daily thyroxine replacement therapy in subclinical hypothyroidism

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is defined as serum thyroid-stimulating hormone (TSH) level above upper limit of normal despite normal levels of serum free thyroxine. According to recommendations, L-thyroxine treatment for hormone replacement therapy should be continued on daily basis. However, some trials have challenged daily regimen for management of hypothyroidism and have suggested dosage scheduling at weekly, twice-a-week or alternate day as possible alternatives having similar effect as for daily regimen.
Methods: Study was prospective randomized cross-over intervention design. Thyroid functions (T3, T4 and TSH) were measured using third generation non-isotopic immunochemiluminescence method using standard protocol. 120 patients with clinically established hypothyroidism were enrolled in study.
Results: Difference in mean TSH levels of group I and group II were not found to be statistically significant at baseline (8.247±2.288 mIU/ml versus 8.210±2.650; p=0.935), at 6 weeks (2.337±1.792 mIU/ml versus 2.843±2.410 mIU/ml; p=0.195) and at 12 weeks (2.508±1.180 mIU/ml versus 2.831±1.200 mIU/ml; p=0.191). Difference in mean T3 levels of group I and group II were not found to be statistically significant at baseline (1.118±0.199 ng/dl versus 1.184±0.187 ng/dl; p=0.061), at 6 weeks (1.266±0.295 ng/dl versus 1.196±0.289 ng/dl; p=0.192) and at 12 weeks (1.121±0.211 ng/dl versus 1.179±0.203 ng/dl; p=0.174). Difference in mean T4 levels group I and group II were not found to be statistically significant at baseline (8.422±2.054 µg/dl versus 7.899±2.333 µg/dl; p=0.196), at 6 weeks (8.852±2.836 µg/dl versus 8.533±2.672 µg/dl; p=0.527) and at 12 weeks (8.159±2.235 µg/dl versus 7.990±2.463 µg/dl; p=0.728).
Conclusions: The findings of present study show that alternate day L-thyroxine is a viable solution for the management of SCH.

Keywords: Subclinical hypothyroidism, TSH, T4, Thyroxine

INTRODUCTION

SCH is defined as a serum TSH level above the upper limit of normal despite normal levels of serum free thyroxine.[1] SCH or mild thyroid failure is a common problem, with a prevalence of 3% to 8% in the population without known thyroid disease.[2,3] The prevalence increases with age and is higher in women.[2] After the sixth decade of life, the prevalence in men approaches that of women, with a combined prevalence of 10%.[2] Antithyroid antibodies can be detected in 80% of patients with SCH and 80% of patients with SCH have a serum TSH of less than 10 mIU/l.[3,4]

The consequences of SCH are variable at several levels and may depend on the duration and the degree of elevation of the serum TSH. Although various studies have suggested it to be a cardiovascular risk factor, yet a

number of important questions about SCH remain, including whether it increases cardiovascular (CV) risk or mortality, whether it negatively influences metabolic parameters and whether it should be treated with L-thyroxine.[5-10] The effect of T4 replacement on lipids is uncertain. However, in several randomized trials of patients with SCH treated with T4 versus placebo, serum total and LDL cholesterol and apoprotein B-100 concentrations decreased significantly, whereas serum HDL cholesterol, triglyceride and lipoprotein (a) concentrations did not change.[11-14]

According to current recommendations, the L-thyroxine treatment regimen for hormone replacement therapy should be continued on a daily basis, however, some trials have challenged the daily regimen for management of hypothyroidism and have suggested dosage scheduling at weekly, twice-a-week or alternate day as the possible alternatives having similar effect as for daily regimen.[15-18] Thyroid hormone is a highly protein bound hormone (>99%) and has prolonged half-life therefore it can be considered suitable for dosing at longer duration. Daily life-long administration may be quite burdensome for some families and can lead to non-adherence to therapy. In a recent observation on hypothyroid patients, non-compliance was suggested to be the most common cause of lack of adequate response to thyroxine replacement therapy. Longer dosing intervals might help to improve compliance too.

Although, these studies build preliminary evidence, our study aimed to affirm the effect of alternate day thyroxine replacement therapy on thyroid function hormones with that of daily thyroxine replacement therapy at designated up intervals in patients of SCH.

METHODS

The study was conducted at department of medicine, Vivekananda Polyclinic and Institute of Medical Sciences (VPIMS), Lucknow in collaboration with King George's Medical University, Lucknow from September 2014 to October 2015. Both were tertiary care hospital catering to a diverse demography of patients in and around Lucknow, having state of the art-infrastructure and multi-specialty facilities. Cases were enrolled from patients of SCH attending the outpatient department/endocrinology clinic of VPIMS and King George Medical University, Lucknow.

The study was prospective randomized cross-over study design. The sample size was calculated using the formula suggested by Snedecor and Cochran 20 to prove the hypothesis. Sample size was calculated to be 120. Patients with clinically established SCH (TSH levels >4.67 µIU/ml and T3, T4 levels within normal range), patients providing valid informed consent for participation, patients in age group 15-50 years were included in the study. All pregnant women, critically ill patients, patients with irregularity in their drug intake were excluded from the study.

Study interventions

The present study was conducted as a cross-over intervention study. All the patients enrolled in the study were randomly allocated to one of the two study groups as follows:

Group I (n=60): In these patients, regimen of 25 µg thyroxine daily was given till 6 weeks. After six weeks, the patients were shifted to double dose (50 µg) alternate day therapeutic regimen till the end of subsequent six weeks.

Group II (n=60): In these patients, double dose (50 µg) alternate day thyroxine replacement therapeutic regimen was applied and continued till six weeks. After six weeks, the patients were shifted to a regimen of 25 µg daily thyroxine replacement therapy till the end of subsequent six weeks (Table 1).

Randomisation was done by computer generated numbers and the reference range of T3 0.79-1.49 ng/ml, T4: 4.5-12.00 µg/dl, TSH: 0.49-4.67µIU/ml. Outcome of interest like baseline measurement of thyroid functions, fasting lipid profile, blood sugar, BMI and blood pressure was done. Repetition of above measurements at 6 weeks and 12 weeks was done.

Thyroid functions (T3, T4 and TSH) were measured using the third generation non-isotopic immunochemiluminescence method using the standard protocol as indicated in the kit.

According to the protocol of study, if a patient on alternate day thyroxine regimen developed any complication considered to be result of inadequate thyroxine replacement or showed any clinical symptoms of hypothyroidism/hyperthyroidism, then the patient was exempted from the study and treated accordingly. The statistical analysis was done using Statistical package for social sciences (SPSS) version 15.0 statistical analysis software. The values were represented in number (%) and mean±SD. The study was approved from institutional ethical committee. Informed consent was obtained from all the participants. The participation in the study was entirely voluntary giving the patient right to withdraw from study whenever he/she wishes to do so.

RESULTS

These 120 patients of SCH were randomly divided in two groups (Table 1). Sixty patients were enrolled in each group with different management protocols. Sixty patients who were subjected to 25 µg thyroxine daily for first 6 weeks and thereafter shifted 50 µg thyroxine alternate day till next 6 weeks were classified as group I while rest 60 patients were subjected to 50 µg thyroxine

alternate day for 6 weeks thereafter shifted to 25 µg thyroxine daily for next 6 weeks were classified as group II.

Table 1: Groupwise distribution of study population (n=120).

Group	Description	No. of patients	Percentage
Group I	25 µg thyroxine daily was given till 6 weeks thereafter shifted to double dose i.e. 50 µg thyroxine alternate day till next 6 weeks	60	50.00
Group II	50 µg thyroxine alternate day till 6 weeks thereafter shifted to 25 µg daily for next 6 weeks	60	50.00
Total		120	100.00

Table 2: Between group comparison of age profile of study population.

Age group (years)	Group I (n=60)		Group II (n=60)		Total (n=120)	
	No.	**%**	**No.**	**%**	**No.**	**%**
≤20	8	13.33	7	11.67	15	12.50
21-30	16	26.67	15	25.00	31	25.83
31-40	20	33.33	23	38.33	43	35.83
41-50	16	26.67	15	25.00	31	25.83
	χ^2=0.340 (df=3); p=0.952					
Min-max (median)	15-50 (33.50)		15-49 (33.50)		15-50 (33.50)	
Mean±SD	32.85±9.93		33.28±9.53		33.07±9.69	

Patients included in the study were aged 15-50 years (median age 33.50 years). Mean age of patients was 33.07±9.69 years. Proportion of patients of group I was higher as compared to group II in age groups ≤20 years (13.33% versus 11.67%), 21-30 years (26.67% versus 25.00%) and 41-50 years (26.67% versus 25.00%) while proportion of patients of group II was higher as compared to group I age group 31-40 years (38.33% vs. 33.33%). Difference in age of patients of group I and group II was not found to be statistically significant (p=0.952) (Table 2).

Out of 120 patients enrolled in the study, majority were females (n=101; 84.17%) and rest 19 (15.83%) were males. Female:male ratio in the present study was 1:0.19. Though proportion of males was higher in ggroup II (21.67%) as compared to group I (10.00%) and proportion of females was higher in group I (90.00%) as compared to group II (78.33%) but difference in gender of patients of group I and group II was not found to be statistically significant (p=0.080) (Table 3).

Table 3: Between group comparison of gender of study population.

Gender	Group I (n=60)		Group II (n=60)		Total (g=120)	
	No	%	No	%	No	%
Female	54	90.00	47	78.33	101	84.17
Male	6	10.00	13	21.67	19	15.83
F:M	1:0.11		1:0.28		1:0.19	
	χ^2=3.064 (df=1); p=0.080					

At baseline, mean TSH levels of patients of group I were found to be higher than that of group II while at 6 weeks and at 12 weeks mean TSH levels of patients of group II were found to be higher than that of group I. Difference in mean TSH levels of patients of group I and group II were not found to be statistically significant at baseline (8.247±2.288 mIU/ml versus 8.210±2.650; p=0.935), at 6 weeks (2.337±1.792 mIU/ml versus 2.843±2.410 mIU/ml; p=0.195) and at 12 weeks (2.508±1.180 mIU/ml versus 2.831±1.200 mIU/ml; p=0.191) (Table 4).

At baseline and at 12 weeks, mean T3 levels of patients of group II were found to be higher than that of group I while at 6 weeks, mean T3 levels of patients of group I were found to be higher than that of group II. Difference in mean T3 levels of patients of group I and group II were not found to be statistically significant at baseline (1.118±0.199 ng/dl versus 1.184±0.187 ng/dl; p=0.061), at 6 weeks (1.266±0.295 ng/dl versus 1.196±0.289 ng/dl; p=0.192) and at 12 weeks (1.121±0.211 ng/dl versus 1.179±0.203 ng/dl; p=0.174).

At baseline, 6 weeks and at 12 weeks, T4 levels of patients of group I were found to be higher than that of group II. Difference in mean T4 levels of patients of group I and group II were not found to be statistically significant at baseline (8.422±2.054 µg/dl versus 7.899±2.333 µg/dl; p=0.196), at 6 weeks (8.852±2.836 µg/dl versus 8.533±2.672 µg/dl; p=0.527) and at 12 weeks (8.159±2.235 µg/dl versus 7.990±2.463 µg/dl; p=0.728).

DISCUSSION

Thyroid diseases are arguably, among the commonest endocrine disorders worldwide. India too, was no exception.

According to a projection from various studies on thyroid disease, it had been estimated that about 42 million people in India suffer from thyroid diseases.[21] The prevalence of hypothyroidism in the developed world was about 4-5%. The prevalence of SCH in the developing world was about 4-5%.[22,23] Cross-sectional studies from India indicated its prevalence to range from

9.27-10.95% with majority of affected people having SCH.[24-26]

Table 4: Between group comparison of thyroid profile of study population.

Group		No. of patients	Min.	Max.	Median	Mean	SD	
TSH mIU/ml								
Baseline	Group I	60	5.14	16.49	8.04	8.247	2.288	't'=0.082; p=0.935
	Group II	60	5.10	17.85	7.69	8.210	2.650	
	Total	120	5.10	17.85	7.86	8.229	2.465	
6 weeks	Group I	60	0.04	7.76	1.88	2.337	1.792	't'=-1.305; p=0.195
	Group II	60	0.08	11.46	2.57	2.843	2.410	
	Total	120	0.04	11.46	2.17	2.590	2.130	
12 weeks	Group I	48	0.63	4.62	2.60	2.508	1.180	't'=-1.317; p=0.191
	Group II	46	0.59	4.57	3.01	2.831	1.200	
	Total	94	0.59	4.62	2.74	2.667	1.193	
T3 (ng/dl)								
Baseline	Group I	60	0.79	1.48	1.12	1.118	0.199	't'=-1.894; p=0.061
	Group II	60	0.83	1.48	1.22	1.184	0.187	
	Total	120	0.79	1.48	1.15	1.151	0.195	
6 weeks	Group I	60	0.80	1.96	1.29	1.266	0.295	't'=1.312; p=0.192
	Group II	60	0.80	1.89	1.17	1.196	0.289	
	Total	120	0.80	1.96	1.19	1.231	0.293	
12 weeks	Group I	48	0.79	1.48	1.13	1.121	0.211	't'=-1.370; p=0.174
	Group II	46	0.82	1.46	1.21	1.179	0.203	
	Total	94	0.79	1.48	1.16	1.149	0.207	
T4 (µg/dl)								
Baseline	Group I	60	4.76	11.85	8.19	8.422	2.054	't'=1.301; p=0.196
	Group II	60	4.57	11.77	8.01	7.899	2.333	
	Total	120	4.57	11.85	8.08	8.161	2.204	
6 weeks	Group I	60	4.62	14.83	8.52	8.852	2.836	't'=0.634; p=0.527
	Group II	60	4.66	14.87	8.00	8.533	2.672	
	Total	120	4.62	14.87	8.30	8.693	2.748	
12 weeks	Group I	48	4.66	11.66	8.89	8.159	2.235	't'=0.349; p=0.728
	Group II	46	4.56	11.99	7.50	7.990	2.463	
	Total	94	4.56	11.99	8.35	8.076	2.338	

Thyroid hormones are recognized as catabolic hormones and they regulate various processes of metabolism including the synthesis, mobilization, and breakdown of lipids. Hypothyroidism was reported to be associated with an increased risk for cardiovascular disease.[27,28] Thyroid was also considered to have an effect on reproductive hormones and is often associated with diseases like polycystic ovarian syndrome.[29] It also had an impact on psychological and psychiatric well-being of the individual.[30] SCH in children had also been shown to be associated with intellectual, cognitive and physical growth impairment.[31,32]

In present study, age of patients ranged from 15 to 50 years as per the inclusion criteria laid down. However, majority of cases were in the age range 31 to 50 years (61.66%). In a large epidemiological study from India, a bimodal age distribution of patients was observed with peak incidence in 36-45 years and >55 years of age. In present study, we did not include any patient aged >50 years and hence, the age distribution was in accordance with the population incidence within 50 years of age. Close to the findings of present study, Deshmukh et al in a study from Mumbai also reported the maximum prevalence (74%) in 35-54 years age group.[33] Thus age profile of our patients was representative of the population.

Majority of study population was female (84.17%). The gender ratio was 0.19. Almost all the epidemiological studies show females to be more affected by SCH as compared to males. In a study, reviewing the global epidemiology of SCH, it was reported to be 10 times more common in women than in men. In different epidemiological studies from India, the gender ratio was not such skewed. In a study from Mumbai, the male to female ratio was 0.26:1. In another study from Kashmir valley, the male to female ratio was 0.22, which was slightly higher than that observed in present study. However, another study from India reported only a marginal difference in prevalence of SCH between males and females with a male to female ratio being 0.82. In general, the gender profile of present study was a reflection of different epidemiological studies showing a dominance of females over males. On comparing the age and gender profile between two randomized group, the

difference was not found to be significant statistically, thus showing that the two groups were matched and comparable.

At baseline mean TSH, T3 and T4 levels in group I were 8.247±2.288 mIU/ml, 1.118±0.199 ng/dl and 8.422±2.052 µg/dl respectively and in group II were 8.210±2.650 mIU/ml, 1.184±0.187 ng/dl and 7.899±2.333 µg/dl respectively, before crossover alternate day regimen group. On evaluating the data statistically, there was no significant difference between two groups ($p>0.05$) for any of the thyroid profile components. Indicating both the groups was matched for thyroid profile at the time of inclusion in the study.

After six weeks, mean TSH, T3 and T4 levels were 2.337±1.792 mIU/ml, 1.266±0.187 ng/dl and 8.852±2.836 µg/dl respectively in group I (before crossover daily regimen group) and 2.843±2.410 mIU/ml, 1.196±0.289 ng/dl and 8.533±2.672 µg/dl respectively in group II (before crossover alternate day regimen group). On evaluating the data statistically, there was no significant difference between two groups ($p>0.05$) for any of the thyroid profile components. On evaluating the change in thyroid functions following intervention, for TSH both the groups showed a significant change depicting 71.66% fall in TSH levels in group I (before crossover daily regimen) and 65.38% fall in TSH levels in group II (before crossover alternate day regimen). For T3 in group I (before crossover daily regimen) showed a percentage increase of 13.31% whereas in group II (before crossover alternate day regimen) showed a percentage increase of 1% only. On evaluating the change statistically, the change in before crossover daily regimen group was found to be significant. For T4, before crossover daily regimen and alternate day regimen groups showed an increment of 5.11 and 8.02% respectively but in both the groups, the change was not significant statistically.

These findings in turn imply that after 6 weeks of L-thyroxine treatment, both the groups had equivalent effect on thyroid profile. Although, the extent of change in T3 values was a bit higher in group I (before crossover daily regimen), yet it did not bring about a change in clinical status of the patients.

On evaluating the changes in thyroid function hormones six weeks after the crossover (12 weeks after the initiation of study), mean TSH, T3 and T4 levels were 2.508±1.18 mIU/ml, 1.121±0.211 ng/dl and 8.159±2.748 µg/dl respectively in after crossover alternate day regimen group and 2.831±1.200 mIU/ml, 1.179±0.203 ng/dl and 7.990±2.463 µg/dl respectively in after crossover daily regimen group. On evaluating the data statistically, there was no significant difference between two groups ($p>0.05$) for any of the thyroid profile components. On evaluating the change in thyroid function tests between six and 12 weeks intervals statistically no change was observed in either of two groups. The findings in effect show that both the drug regimens acted similarly offering a significant reduction in TSH levels with either of two regimens while at the same time cross-over did not affect the efficiency of either of two groups in their ability to maintain the thyroid function status. These findings suggest that rescheduling did not affect the efficacy of treatment as far as their effect on thyroid functions, as observed through thyroid function test status, was concerned.

The effect of rescheduling of L-thyroxine treatment to alternate and weekly intervals has also been studied previously. In a study of children with congenital hypothyroidism, Dayal et al observed similar efficacy of daily and alternate day regimen on thyroid function hormones (T3, T4 and TSH) at three follow up intervals, one month apart.[18] However, the study did not use a crossover design like ours. In another study that compared daily versus weekly dosages of L-thyroxine, that also used a cross-over design like ours, no significant difference in fasting TSH and T3 levels were observed between weekly and daily regimens. Although, at the end of 6 weeks, T4 levels of daily regimen patients were higher as compared to the weekly dose patients. Following crossover, though an increase in TSH levels of post-cross over weekly regimen group and a decrease in TSH levels of post-cross over daily regimen group was observed, yet despite these differences, the difference between two regimens was not significant statistically. In two earlier studies, Taylor et al and Grebe et al found an equivalent efficacy of twice-weekly and once-weekly L-thyroxine regimen.[16,17]

One of the important difference in previous studies and current study was that in present study, all the patients were subclinically hypothyroid at the time of enrolment whereas in all the previous studies the patients were euthyroid at the time of inclusion.[16-18] The findings in present study thus show that alternate day regimen can be successfully used with equal efficacy in newly diagnosed hypothyroid cases too for the treatment of SCH.

One of the limitation in present study was that we could evaluate the thyroid functions on 6 weeks intervals only, however, some previous studies have evaluated the short term changes in thyroid hormones between two groups.[16,17] In their study, Taylor et al averaged the day 1, 2, 3, 4 and 5 thyroid hormone levels between twice-weekly and daily thyroxine replacement therapy and found the trends of two groups to be similar.[16]

Although, one of the limitation of their study was sample size as they had used the cross-over design in 7 women only. On the other hand, Grebe et al in their study randomized 12 patients to two groups of 7 and 5 patients and compared the 24-hr post-drug intake thyroid hormone levels and found that up to 8 hours post-drug intake thyroid hormone levels in general showed a significantly higher mean trend in weekly regimen as compared to daily regimen.[17]

In present study, we did not make any such assessment because we were using an alternate day regimen at the double dose (50 µg) as compared to daily dose (25 µg) which did not make a much difference as a 7 times higher dose which was administered in the previous studies.[17] Moreover, in previous study using twice weekly design, which is somewhat close to ours, no such fluctuations in thyroid hormone levels were observed. Given the level of fluctuations in thyroid hormone levels in previous studies using once-weekly regimen at almost 7 times higher dose as compared to daily regimen, the implications could be more severe at such high dosage. Unfortunately, the previous studies using the change in scheduling of drug have been conducted on a very small number of patients and were just pilot studies. The strength of the present study lies in the fact that it was carried out on a substantially larger population and achieved the comparable results for two alternate scheduling regimens.

In present study clinical outcome of two regimens was evaluated in terms of change in lipid profile. It was observed that both the regimens regularized these parameters with equal efficacy with no significant difference between the two groups. In their study, Grebe et al also observed no significant difference in clinical profile of patients in terms of clinical signs and symptoms at the end of six weeks as well as for lipid, liver, bone and hemodynamic parameters at 0 hr and 8 hr after drug intake except for serum cholesterol levels which were significantly higher in weekly regimen as compared to that in daily regimen.[17] In present study, we did not find any such difference between two regimens, and could attribute this finding to the fact that we kept the spacing between two dosages at a maximum of 48 hours. Keeping in view the half-life of L-thyroxine to be close to 7 days, the weekly regimen might have some efficacy issues. Dayal et al on the other hand, in their study, found total cholesterol levels to be significantly lower in alternate day regimen as compared to daily regimen but did not see a significant difference between two groups at the end of six weeks of intervention.[18] However, it must be noted that Dayal et al did not have statistically matched groups even at baseline.[18] In fact in their study, for most of the biochemical parameters (AST, ALT, HDL, LDL, and TC), a significant difference between two groups existed on the baseline itself.

Thus, the findings of the present study, in the light of previous studies show that alternate day L-thyroxine is a viable solution for the management of SCH. As such, the findings of present study opened the doors for a debate to start alternative scheduling strategy for those patients who find it unable to comply to a daily regimen of L-thyroxine. It is probably the largest series exploring the possibility of an alternative scheduling of L-thyroxine. In order to be safe, we expanded the dosing gap to a minimum from 24 hours to 48 hours, however, and experimented in subclinically hypothyroid patients with deranged TSH and found comparable results. This is a positive finding that opens up the doors to evaluate the efficacy of drugs in other combinations such as twice weekly or weekly regimens. Further studies on similar scheduling are also recommended to corroborate the findings of present study. These findings are a single institutional data of the same city, on small number of samples, hence the findings have their limitations. Moreover the evaluation of thyroid functional test was done at 6 weeks on follow up visits. So these findings need to be confirmed on higher number of patients in multiple institutions.

CONCLUSION

On the basis of above findings, it could be concluded that both daily as well as alternate day L-thyroxine regimen were equally efficacious in management of SCH. Given the better compliance rate of alternate day regimen, it could be advised as a better alternative to patients for whom compliance of daily dose L-thyroxine is an issue. Further studies on more scheduling combinations are recommended.

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