Original Research Article

A Hospital Based Prospective Study for Comparative Assessment of the Efficacy of Morning Dose Versus Evening Dose Levothyroxine in Hypothyroidism Patients

Ateendra Singh[1], Rajesh Kumar Jangir[2], Jitendra Singh[3*]

[1]Associate Professor, Department of Pharmacology, S. K. Government Medical College, Sikar, Rajasthan, India
[2]Senior Demonstrator, Department of Pharmacology, S. K. Government Medical College, Sikar, Rajasthan, India
[3]Assistant Professor, Department of Pharmacology, Jhalawar Medical College, Jhalawar, Rajasthan, India

Received: 06-10-2021 / Revised: 29-11-2021 / Accepted: 07-12-2021

Abstract

Background: Hypothyroidism is the result of inadequate production of thyroid hormone and the inadequate action of thyroid hormone in target tissues. Hence; the present study was conducted for comparatively assessing the Efficacy of Morning Dose Versus Evening Dose Levothyroxine in Hypothyroidism Patients. **Materials & Methods:** A total of 40 patients with presence of hypothyroidism were enrolled. All the patients were broadly divided into two study groups as follows: Group A- 20 patients who received morning dose of Levothyroxine, and Group B- 20 patients who received evening dose of Levothyroxine. All patients were having Hashimoto's thyroiditis as underlying cause of hypothyroidism. In the process of non-achievement of euthyroidism at the end of 6 weeks, the dose was increased by 25 mcg/day. The study was carried for a time period of 12 weeks. Biochemical variables were analyzed at different time intervals. All the results were recorded and analyzed by SPSS software. **Results:** Mean fT3 levels among the patients of group A at baseline, 8 weeks and 14 weeks was 2.13 pg/mL, 2.85 pg/mL and 3.76 pg/mL respectively. Mean fT3 levels among the patients of group B at baseline, 8 weeks and 14 weeks was 2.11 pg/mL, 2.72 pg/mL and 3.53 pg/mL respectively. Mean fT4 levels among the patients of group A at baseline, 8 weeks and 14 weeks was 0.76 ng/dL, 1.28 mg/dL and 1.69 ng/dL respectively. Mean fT4 levels among the patients of group B at baseline, 8 weeks and 14 weeks was 0.71 ng/dL, 1.35 mg/dL and 1.62 ng/dL respectively. Mean TSH levels among the patients of group A at baseline, 8 weeks and 14 weeks was 83.46 mIU/L, 23.81 mIU/L and 6.28 mIU/L respectively. Mean TSH levels among the patients of group B at baseline, 8 weeks and 14 weeks was 79.36 mIU/L, 21.98 mIU/L and 5.12 mIU/L respectively. Non-significant results were obtained while comparing the various biochemical variables among the two study groups at different time intervals. **Conclusion:** Whether given during morning or evening, the drug has same bioavailability and metabolism.

Keywords: Hypothyroidism, Levothyroxine, Hospital.

Introduction

Hypothyroidism is the result of inadequate production of thyroid hormone and the inadequate action of thyroid hormone in target tissues. Primary hypothyroidism is the principal cause of hypothyroidism, but other causes include central deficiency of thyrotropin-releasing hormone (TRH) or thyroid-stimulating hormone (TSH). Subclinical hypothyroidism (SCH) is present when there is a minimally elevated TSH and normal free thyroxin (FT4) level without clinical manifestation or minimal presentation. Hypothyroidism may be either clinical/overt, with elevation in the TSH and low levels of FT4, or subclinical, with normal levels of FT4 and elevated level of TSH. Hypothyroidism can arise as primary from the thyroid gland when there is a defect in thyroid hormone synthesis and release centrally from the hypothalamic-pituitary-thyroid axis when there is a defect in either TRH or TSH signaling to the thyroid. The condition may also be transient or permanent. Iodine deficiency is the most common cause of hypothyroidism worldwide. In people living in iodine-replete areas, the causes are congenital, spontaneous because of chronic autoimmune disease (primary atrophic hypothyroidism, Hashimoto's thyroiditis) or iatrogenic due to goitrogens, drugs, or destructive treatment for hyperthyroidism[1-3].

**Correspondence*
Dr. Jitendra Singh
Assistant Professor, Department of Pharmacology, Jhalawar Medical College, Jhalawar, Rajasthan, India.
E-mail: jitendra0999@gmail.com

Because the prevalence of primary hypothyroidism is high among the general population, levothyroxine sodium is one of the most prescribed medications. Absorption of levothyroxine is approximately 70% to 80% and occurs in the small bowel. There is consensus that levothyroxine should be taken before breakfast to prevent interference of its intestinal uptake by food or other medications[4-6]. Hence; the present study was conducted for comparatively assessing the Efficacy of Morning Dose Versus Evening Dose Levothyroxine in Hypothyroidism Patients.

Materials & Methods

The present study was conducted for comparatively assessing the Efficacy of Morning Dose Versus Evening Dose Levothyroxine in Hypothyroidism Patients. A total of 40 patients with presence of hypothyroidism were enrolled. All the patients were broadly divided into two study groups as follows: Group A- 20 patients who received morning dose of Levothyroxine, and Group B- 20 patients who received evening dose of Levothyroxine. All patients were having Hashimoto's thyroiditis as underlying cause of hypothyroidism. After explaining the study protocol, written consent was obtained from all the patients. None of the patients used medication known to interfere with levothyroxine absorption, nor were they known to have gastro-intestinal disease. In the process of non-achievement of euthyroidism at the end of 6 weeks, the dose was increased by 25 mcg/day. The study was carried for a time period of 12 weeks. Biochemical variables were analyzed at different time intervals. All the results were recorded and analyzed by SPSS software. Chi-square test and

student t test was used along with One way ANOVA for analysis of level of significance.

Results

Mean age of the patients of group A and group B was 45.5 years and 46.9 years respectively. Majority of the patients of both the study groups were males. Mean fT3 levels among the patients of group A at baseline, 8 weeks and 14 weeks was 2.13 pg/mL, 2.85 pg/mL and 3.76 pg/mL respectively. Mean fT3 levels among the patients of group B at baseline, 8 weeks and 14 weeks was 2.11 pg/mL, 2.72 pg/mL and 3.53 pg/mL respectively. Mean fT4 levels among the patients of group A at baseline, 8 weeks and 14 weeks was 0.76 ng/dL, 1.28 mg/dL and 1.69 ng/dL respectively. Mean fT4 levels among the patients of group B at baseline, 8 weeks and 14 weeks was 0.71 ng/dL, 1.35 mg/dL and 1.62 ng/dL respectively. Mean TSH levels among the patients of group A at baseline, 8 weeks and 14 weeks was 83.46 mIU/L, 23.81 mIU/L and 6.28 mIU/L respectively. Mean TSH levels among the patients of group B at baseline, 8 weeks and 14 weeks was 79.36 mIU/L, 21.98 mIU/L and 5.12 mIU/L respectively. Non-significant results were obtained while comparing the various biochemical variables among the two study groups at different time intervals.

Table 1: Biochemical variables at different time intervals

Biochemical variables	Group A			Group B		
	Baseline	8 weeks	14 weeks	Baseline	8 weeks	14 weeks
fT3 (pg/mL)	2.13	2.85	3.76	2.11	2.72	3.59
fT4 (ng/dL)	0.76	1.28	1.69	0.71	1.35	1.62
TSH (mIU/L)	83.46	23.81	6.20	79.36	21.98	5.12

Table 2: Comparison biochemical variables in between both the study groups

Biochemical variable	Group A Versus group B	Group A Versus group B	Group A Versus group B
	Baseline	8 weeks	14 weeks
fT3 (pg/mL)	0.12	0.46	0.71
fT4 (ng/dL)	0.28	0.84	0.16
TSH (mIU/L)	0.34	0.39	0.24

Discussion

The prevalence of thyroid dysfunction increases with age. Physiological changes due to the aging process could impact hypothyroidism treatment. In older populations, pharmacokinetics might be modified by gastrointestinal aging and decreases in body water content, serum albumin, hepatic biotransformation, and renal clearance. Levothyroxine is a synthetic derivative (levorotatory isomer) of thyroxine. Its ionization state and dissolution are influenced by gastric pH[6-9]. Hence; the present study was conducted for comparatively assessing the Efficacy of Morning Dose Versus Evening Dose Levothyroxine in Hypothyroidism Patients.

Mean age of the patients of group A and group B was 45.5 years and 46.9 years respectively. Majority of the patients of both the study groups were males. Mean fT3 levels among the patients of group A at baseline, 8 weeks and 14 weeks was 2.13 pg/mL, 2.85 pg/mL and 3.76 pg/mL respectively. Mean fT3 levels among the patients of group B at baseline, 8 weeks and 14 weeks was 2.11 pg/mL, 2.72 pg/mL and 3.53 pg/mL respectively. Mean fT4 levels among the patients of group A at baseline, 8 weeks and 14 weeks was 0.76 ng/dL, 1.28 mg/dL and 1.69 ng/dL respectively. In a previous study conducted by Rajput R et al, authors evaluated the efficacy of morning versus evening Dose of Levothyroxine in Treatment of Hypothyroidism. 152 drug naïve primary hypothyroid patients were divided into morning (Group 1) and evening (Group 2) dosing group and evaluated for change in biochemical profile, physical functioning and Quality of Life during the course of 12 weeks of study. At the end of 12 weeks 70 (90.90%) subjects in Group 1 and 72 (96%) in Group 2 achieved euthyroidism. On evaluation clinical symptoms and total clinical scores improved in both the groups at the end of 6 and 12 weeks. Significant improvement in thyroid profile was seen in both the groups at the end of 6 and 12 weeks (P value <.0001). On intergroup comparison, no significant difference in thyroid profile was seen at 6 and 12 weeks between the morning and the evening dose group. Similar dose of levothyroxine was required to achieve euthyroidism in both the groups. Though an early restoration of euthyroidism was seen in evening group, the difference when compared to the morning group was not statistically significant. On assessment of QoL, statistically significant improvement in various parameters was seen in both the groups. Hence, from the study they inferred that evening dose is as efficacious as morning dose and provides an alternate dosing regimen[10].

In the present study, Mean fT4 levels among the patients of group B at baseline, 8 weeks and 14 weeks was 0.71 ng/dL, 1.35 mg/dL and 1.62 ng/dL respectively. Mean TSH levels among the patients of group A at baseline, 8 weeks and 14 weeks was 83.46 mIU/L, 23.81 mIU/L and 6.28 mIU/L respectively. Mean TSH levels among the patients of group B at baseline, 8 weeks and 14 weeks was 79.36 mIU/L, 21.98 mIU/L and 5.12 mIU/L respectively. Non-significant results were obtained while comparing the various biochemical variables among the two study groups at different time intervals. Nienke Bolk et al conducted a study to ascertain if levothyroxine intake at bedtime instead of in the morning improves thyroid hormone levels, among 105 consecutive patients with primary hypothyroidism at Maasstad Hospital Rotterdam in the Netherlands. Patients were instructed during 6 months to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Ninety patients completed the trial and were available for analysis. Compared with morning intake, direct treatment effects when levothyroxine was taken at bedtime were a decrease in thyrotropin level of 1.25 mIU/L (95% confidence interval [CI], 0.60-1.89 mIU/L; P < .001), an increase in free thyroxine level of 0.07 ng/dL (0.02-0.13 ng/dL; P = .01), and an increase in total triiodothyronine level of 6.5 ng/dL (0.9-12.1 ng/dL; P = .02) (to convert thyrotropin level to micrograms per liter, multiply by 1.0; free thyroxine level to picomoles per liter, multiply by 12.871; and total triiodothyronine level to nanomoles per liter, multiply by 0.0154). Secondary outcomes, including quality-of-life questionnaires (36-Item Short Form Health Survey, Hospital Anxiety and Depression Scale, 20-Item Multidimensional Fatigue Inventory, and a symptoms questionnaire), showed no significant changes between morning vs bedtime intake of levothyroxine[11].

Conclusion

From the above results, the authors concluded that whether given during morning or evening, the drug has same bioavailability and metabolism.

References

1. Hoogwerf BJ, Nuttall FQ. Long-term weight regulation in treated hyperthyroid and hypothyroid subjects. Am J Med. 1984; 76(6):963-70.
2. Roos AL, Rasker SP, van Domburg RTT, Ijssen JP, Berghout A. The starting dose of levothyroxine in primary hypothyroidism treatment: a prospective, randomized, double-blind trial. Arch Intern Med. 2005; 165(15):1714-20.
3. Huynh TGB, Nayak B, Loh J, Soldin S, Jonklaas J. Timing of levothyroxine administration affects serum thyrotropin concentration. Journal of Clinical Endocrinology & Metabolism. 2009; 94(10):3905–12.
4. Bolk N, Visser TJ, Nijman J, Jongste IJ, Tijssen JGP, Berghout A. Effects of evening vs morning levothyroxine intake. Archives of Internal Medicine. 2010; 170(22):1996–2003.
5. Brabant G, Prank K, Ranft U et al. Physiological regulation of circadian and pulsatile thyrotropin secretion in normal man and woman. Journal of Clinical Endocrinology and Metabolism. 1990; 70(2):403–9.
6. Adriaanse R, Romijn JA, Endert E, Wiersinga WM. The nocturnal thyroid-stimulating hormone surge is absent in overt, present in mild primary and equivocal in central hypothyroidism. Acta Endocrinologica. 1992; 126(3):206–212.
7. Scanlan TS: 3-iodothyronamine (T1AM): a new player on the thyroid endocrine team? Endocrinology. 2009; 150(3):1108-11.
8. Appelhof BC, Fliers E, Wekking EM et al. Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. J Clin Endocrinol Metab. 2005; 90(5):2666-74.
9. Escobar-Morreale HF, Obregón MJ, Escobar del Rey F, Morreale de Escobar G. Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats. J Clin Invest. 1995; 96(6):2828-38.
10. Rajput R, Chatterjee S, Rajput M. Can Levothyroxine Be Taken as Evening Dose? Comparative Evaluation of Morning versus Evening Dose of Levothyroxine in Treatment of Hypothyroidism. J Thyroid Res. 2011; 2011:505239.
11. Nienke Bolk et al. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. Arch Intern Med. 2010; 170(22):1996-2003.

Conflict of Interest: Nil
Source of support:Nil