

Comparison of Treatment Response Achieved by Tablet Splitting Versus Whole Tablet Administration of Levothyroxine in Patients with Thyroid Cancer

Ramin Ashrafpour¹, Narjess ayati^{2*}, Ramin Sadeghi², Samira Zare Namdar², Nayyereh Ayati³, Somayyeh Ghahremani², Seyed Rasoul Zakavi²

¹ School of medicine, Mashhad University of Medical Sciences, Mashhad, Iran

² Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

³ Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of medical sciences, Tehran, Iran

ARTICLE INFO

Article type:
Original article

Article history:
Received: 10 Oct 2017
Revised: 30 Dec 2017
Accepted: 15 Jan 2018

Keywords:
Differentiated thyroid cancer
Levothyroxine
Suppressive therapy
Tablet splitting
TSH

ABSTRACT

Objective(s): TSH suppression by Levothyroxine consumption is a mainstay of thyroid cancer treatment. Tablet-splitting is a worldwide approach in dose adjustment in patients. However, it is highly recommended to evaluate the validity of tablet splitting for each distinctive drug by clinical trials before routinely using tablet halves in clinical practice. In this study we compared the effect of 150 µg dose of Levothyroxine by use of a 100 and a 50 µg tablets or one and half 100 µg tablets in Differentiated thyroid cancer (DTC) patients.

Methods: One hundred DTC patients treated with one and half 100 µg Levothyroxine tablets were randomly divided into two groups. The first group continued taking medication as before and the second group received the same daily dose by taking one 100 and one 50 microgram Levothyroxine tablets. The mean changes in TSH and T3 levels and patients weight were compared between the groups.

Results: 91 patients completed the study. Levothyroxine consumption pattern, age, gender distribution, weight and TSH levels were comparable between groups at the beginning of the study. The mean change of body weights, serum levels of T3 and TSH showed no significant difference between groups in different time points during the study ($P > 0.05$).

Conclusion: This study showed similar efficacy of tablet splitting and two tablets administration for Levothyroxine; however, patients preferred two tablets at the end of the study. It can be concluded that tablet splitting can be used as an alternative way when the 50 µg tablet is not available.

► Please cite this paper as:

Ashrafpour R, Ayati N, Sadeghi R, Zare Namdar S, Ayati N, Ghahremani S, Zakavi SR. Comparison of Treatment Response Achieved by Tablet Splitting Versus Whole Tablet Administration of Levothyroxine in Patients with Thyroid Cancer. Asia Ocean J Nucl Med Biol. 2018; 6(2): 108-112. doi: 10.22038/aojnmb.2018.26793.1187

Introduction

Differentiated thyroid cancer is the most common malignancy of endocrine system (1-3) and its prevalence is increasing worldwide. As

this pathology mostly occurs in the middle age population and it has excellent prognosis, the patients are expected to live for a long time after

* Corresponding author: Narjess Ayati, Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +985138012782; Fax: +985138400494; Email: ayatin@mums.ac.ir
© 2018 mums.ac.ir All rights reserved.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

diagnosis. Replacement or suppressive therapy with Levothyroxine is the standard therapeutic protocol in these patients following total thyroidectomy and radioactive iodine therapy. The suggested dose of Levothyroxine in an adult DTC patient is 1.6 to 2 microgram per kilogram of body weight ($\mu\text{g}/\text{kg}$) (3), equivalent to 100 to 200 micrograms of Levothyroxine on a daily basis.

Tablet splitting is a popular way of daily dose adjustment with better social acceptability, more convenience, and cost saving for the patient and society compared to simultaneous use of two tablets with different doses.(4, 5) However, this method is not suitable in all patients or for all drugs and it may result in inaccurate dosing.(6) It has been strongly recommended to assess the splitting impact of each individual medication by clinical trials before their routine use.(7) This issue is of greater concern in the medications with narrow therapeutic index such as Levothyroxine. Although lots of trials have been done on appropriateness of tablet splitting in different medications (8-13) and different underlying diseases (14-19), to the extent of our knowledge, there is no published study regarding the clinical impact of Levothyroxine tablet splitting in the literature. Only an in-vitro assessment has been done on uniformity content of splits tablets of Levothyroxine Sodium which showed high probability of uniformity failure in tablet halves. (20) The aim of this study is to compare the effectiveness of tablet splitting with taking two tablets of Levothyroxine in DTC patients.

Methods

One hundred differentiated thyroid cancer patients who were under suppressive therapy with one and a half 100 μg levothyroxine sodium tablets were included in the study. The serum TSH and T3 levels were measured in all patients at baseline, and then they were randomly divided into two groups. The first group continued taking medication as before and the second group received the same daily dose by taking one 100 and one 50 microgram Levothyroxine tablets. Thyroid function tests were repeated at least three weeks later and the results were compared. To ensure consistency of used drug in patients, all tablets used in these patients were produced by the same company (Iran-hormone Company) that is the most common generic form in Iran. Consumption pattern of Levothyroxine tablet and plasma levels of TSH and T3 and the patients' weight were recorded at the beginning and the end of the study and the mean changes in TSH

and T3 levels and weight in both groups were compared. Confounding variables such as time of using medication, and other used medicines were recorded and compared between two groups.

For evaluation of normal distribution of the study variables, Kolmogorov-Smirnov test was used. For comparison of study variables between groups, independent sample t-test was used and level of significance was set at $P < 0.05$.

Results

One hundred DTC patients, 29 male (29%) and 71 female (71%) with the age range of 18 to 76 years (mean \pm SD =41.9 \pm 13.3) were included in the study. Among these 100 patients, 9 (2 cases from group 1 and 7 cases from group 2) were excluded from the study. The cause of exclusion of patients from the first group was discontinuation of drug for repeating radioactive iodine therapy in one of patients and decision for performing diagnostic whole body iodine scan in the other one. The cause of exclusion of patients from second group was discontinuation of drug for treatment evaluation in off-T4 status (2 cases), patient's decision to leave the study (2 cases), no referral after two months and change it to previous form of drug usage (2 cases) and changing the Levothyroxine dose by endocrinologist (1 case). Consequently, 48 patients (52.7%) in group 1 (daily intake of 1.5 levothyroxine 100 μg tablets) and 43 (47.3%) in group 2 (daily consumption of one 50 μg tablet and one 100 μg tablet) completed the assessment.

The mean time interval between two assessments was 78.5 (26 to 175 days) with the standard deviation of 33.6.

All variables in the study had normal distribution and independent sample t-test was used for comparison of variables between groups. 12 (25%) patients in the first and 14 (32.6%) patients in the second group were male ($P=0.42$). The age distribution and initial measured quantities including patients' weight, blood level of TSH and time interval between two tests were similar between the two groups at the beginning of the study (Table 1). T3 plasma level was statistically different between two groups ($P=0.01$) (Table 1).

The Levothyroxine consumption pattern was unchanged in both groups at the first and at the end of the study.

Table 2 shows the dependent variables at baseline and end of study and the comparison of changes between the groups. The mean changes of patients' weight and serum levels of TSH and T3 were not statistically different between two groups and the p values were 0.28, 0.29 and 0.74

Table 1. Comparison of initial variables between two groups

	Range	Group 1 (mean±SD)	Group 2 (mean±SD)	P value
Age (year)	18-76	42.3±13.4	41.5±13.1	0.75
Initial Weight (Kg)	36-101	71.9±9.1	73.0±11.9	0.07
Initial TSH (mU/L)	0.005-3.58	0.31±0.43	0.38±0.66	0.6
Initial TT3 (mU/L)	78-264	130.0±27.3	152.2±36.5	0.01
Time interval between two tests (days)	26-175	82.2±40.9	74.6±23.7	0.29

Table 2. Comparison of variables change at the beginning and end of the study between two groups

	Group 1 (Mean±SD)	Group 2 (Mean±SD)	P value
Weight (Kg)			
W ₀	71.9±9.1	73.0±11.9	0.28
W ₁	72.2±8.9	72.8±12.4	
ΔW (W ₀ -W ₁)	-0.36±2.37	0.28±1.73	
Serum TSH (mU/L)			
TSH ₀	0.31±0.43	0.38±0.66	0.29
TSH ₁	0.21±0.34	0.41±0.69	
ΔTSH (TSH ₀ -TSH ₁)	0.10±0.30	-0.03±0.86	
Serum TT3 (mU/L)			
TT3 ₀	130±27.3	152±36.5	0.74
TT3 ₁	138±33.2	155±38.9	
ΔTT3 (TT3 ₀ -TT3 ₁)	-7.3±39.8	-3.4±52.6	

TSH: Thyroid Stimulating Hormone, TT3: Total T3

respectively (Table 2).

At baseline, twenty patients (25.6%), including ten patients in the first group (23.3%) and ten patients in the second group (28.6%) declared that they prefer using two tablets instead of tablet splitting which was statistically similar between the two groups (P=0.31). The same question was repeated at the end of the study, which the result was unchanged in group 1 while in the

second group 78.6% of patients preferred the use of two tablets (instead of tablet splitting) and this time, the difference between two groups in their consumption preference was statistically significant (P<0.001). Considering the increasing cost of medicines by using two tablets instead of tablet splitting at the rate of 3\$ per year, the question was repeated and there was no change in the preferences of patients (Table 3).

Table 3. Patients preference about method of Levothyroxine consumption at the beginning and end of the study

	No comments	Two tablets (One 100 + one 50 µg LT4 tablets)	Tablet Splitting (1.5 tablets of 100 µg LT4)
Beginning of the study			
All Patients	59%	15.4%	25.6%
Group 1	55.8%	20.9%	23.3%
Group 2	62.9%	8.6%	28.6%
End of the study			
All Patients	37.6%	13%	49.4%
Group 1	55.8%	20.9%	23.3%
Group 2	19%	78.6%	2.4%

Discussion

This study was done to compare the performance of using 1.5 tablets of 100 µg Levothyroxine and the simultaneous using of one 100 and one 50 µg tablets in patients with DTC. To the extent of our knowledge, this is the first study which assessed the efficacy of tablet splitting for Levothyroxine Sodium in clinical practice.

The size, shape and hardness of each kind of drug have influence on uniformity of tablet pieces and stability of blood levels of that medicine (18, 21-23). There is only one study in the literature which evaluated the uniformity of Levothyroxine halves as well as their stability in the laboratory. (20) The study showed similar stability between half and whole Levothyroxine tablets. However as the chemical imaging analysis revealed heterogeneous distribution of content, the potential likelihood of under or over dosage using tablet halves remained a clinical concern. The current study verified the same clinical effect of using each of these two methods in a large group of DTC patients. This finding is of great clinical significance in daily practice from two different aspects including acceptability of tablet splitting for this specific medication (Levothyroxine) as well as its appropriateness in this specific population of thyroid cancer patients. As DTC patients are routinely on suppressive therapy with Levothyroxine, the nervousness and anxiety are common complaints among them (24) which have the potential of interfering with accurate tablet splitting. However, this study showed no significant impact of underlying disease and its complications on tablet splitting accuracy.

Changing in patients' preference after taking levothyroxine in new way (using two tablets) was an interesting observation and showed that among the 22 patients in group 2 which initially had no preferred route of administration, 14 people (63%), preferred it to tablet splitting method after experiencing two tablets taking. This observation was in contrary with previous data which mentioned the convenience consumption as an obvious advantage of tablet splitting. (25-27)

Another mentioned advantage for tablet splitting in the literature is reducing health expenses (4); however at the moment, this point is not important issue for patients in our country due to slight difference in drug costs between these two methods of administration.

Because the patients were assessed under the administration of Levothyroxine, T4 hormone level was not assessed and TSH and T3 levels as

well as patients' weight were used as quantitative variables. A limitation of this study was unchecked fT3 and fT4 levels in patients.

There was no statistically significant difference between two groups in terms of laboratory tests interval; however, the lesser mean interval in the second group is probably due to the limited number of new tablets we provided and personal sensitivity due to being faced with new method of Levothyroxine taking.

In this study, significant change was observed in patient preference after taking two tablets however as the patients were provided with new Levothyroxine tablets (50 microgram) by department without charging, some key preference factors such as cost and availability were not available for assessment.

Conclusion

This study showed similar efficacy of tablet splitting and taking two tablets of Levothyroxine with different doses in DTC patients. It can be concluded that tablet splitting can be used as an alternative way of Levothyroxine administration when the 50 µg tablet is not practically available.

References

1. Zakavi SR, Ayati N, Farahati J, Davachi B. Diffuse skeletal metastasis and low thyroglobulin level in a pediatric patient with papillary thyroid carcinoma. *Indian J Nucl Med.* 2015;30(3):283-5.
2. Zakavi SR. Meta-analysis on successful ablation after low- versus high-dose radioiodine therapy in patients with differentiated thyroid carcinoma. *Clin Nucl Med.* 2016;41(8):674.
3. Haugen BR. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: what is new and what has changed? *Cancer.* 2017; 123(3):372-81.
4. Freeman MK, White W, Iranikhah M. Tablet splitting: a review of the clinical and economic outcomes and patient acceptance. Second of a 2-part series. Part 1 was published in May 2012 (*Consult Pharm* 2012;27:239-53). *Consult Pharm.* 2012;27(6):421-30.
5. Elliott I, Mayxay M, Yeuchaixong S, Lee SJ, Newton PN. The practice and clinical implications of tablet splitting in international health. *Trop Med Int Health.* 2014; 19(7):754-60.
6. Verrue C, Mehuys E, Boussery K, Remon JP, Petrovic M. Tablet-splitting: a common yet not so innocent practice. *J Adv Nurs.* 2011;67(1):26-32.
7. Tablet splitting. *JAMA.* 2014;311(5):521.
8. Chou CL, Hsu CC, Chou CY, Chen TJ, Chou LF, Chou YC. Tablet splitting of narrow therapeutic index drugs:

- a nationwide survey in Taiwan. *Int J Clin Pharm*. 2015;37(6):1235-41.
9. Tahaineh LM, Gharaibeh SF. Tablet splitting and weight uniformity of half-tablets of 4 medications in pharmacy practice. *J Pharm Pract*. 2012;25(4):471-6.
 10. Dormuth CR, Schneeweiss S, Brookhart AM, Carney G, Bassett K, Adams S, et al. Frequency and predictors of tablet splitting in statin prescriptions: a population-based analysis. *Open Med*. 2008;2(3):e74-82.
 11. Vranic E, Uzunovic A. Influence of tablet splitting on content uniformity of lisinopril/hydrochlorothiazide tablets. *Bosn J Basic Med Sci*. 2007;7(4):328-34.
 12. Cook TJ, Edwards S, Gyemah C, Shah M, Shah I, Fox T. Variability in tablet fragment weights when splitting unscored cyclobenzaprine 10 mg tablets. *J Am Pharm Assoc*. 2004;44(5):583-6.
 13. Zhao N, Zidan A, Tawakkul M, Sayeed VA, Khan M. Tablet splitting: product quality assessment of metoprolol succinate extended release tablets. *Int J Pharm*. 2010;401(1-2):25-31.
 14. Nidanapu RP, Rajan S, Mahadevan S, Gitanjali B. Tablet splitting of antiepileptic drugs in pediatric epilepsy: potential effect on plasma drug concentrations. *Paediatr Drugs*. 2016;18(6):451-63.
 15. Abu-Geras D, Hadziomerovic D, Leau A, Khan RN, Gudka S, Locher C, et al. Accuracy of tablet splitting and liquid measurements: an examination of who, what and how. *J Pharm Pharmacol*. 2017;69(5):603-12.
 16. Mascarenhas Starling F, Medeiros-Souza P, Francisco de Camargos E, Ferreira F, Rodrigues Silva A, Homem-de-Mello M. Tablet splitting of psychotropic drugs for patients with dementia: a pharmacoepidemiologic study in a Brazilian sample. *Clin Ther*. 2015;37(10):2332-8.
 17. Quinzler R, Gasse C, Schneider A, Kaufmann-Kolle P, Szecsenyi J, Haefeli WE. The frequency of inappropriate tablet splitting in primary care. *Eur J Clin Pharmacol*. 2006;62(12):1065-73.
 18. Tablet splitting: evaluating appropriateness for patients. *J Am Pharm Assoc*. 2004;44(3):324-5.
 19. Peek BT, Al-Achi A, Coombs SJ. Accuracy of tablet splitting by elderly patients. *JAMA*. 2002;288(4):451-2.
 20. Shah RB, Collier JS, Sayeed VA, Bryant A, Habib MJ, Khan MA. Tablet splitting of a narrow therapeutic index drug: a case with levothyroxine sodium. *AAPS PharmSciTech*. 2010;11(3):1359-67.
 21. Helmy SA. Tablet splitting: is it worthwhile? Analysis of drug content and weight uniformity for half tablets of 16 commonly used medications in the outpatient setting. *J Manag Care Spec Pharm*. 2015;21(1):76-86.
 22. Freeman MK, White W, Iranikhah M. Tablet splitting: a review of weight and content uniformity. *Consult Pharm*. 2012;27(5):341-52.
 23. McDevitt JT, Gurst AH, Chen Y. Accuracy of tablet splitting. *Pharmacotherapy*. 1998;18(1):193-7.
 24. Zakavi SR, Zare NS, Shafiei S, Sadeghi R, Fekri N, Mazloun KZ, et al. Which complaint has the most clinical effect on quality of life of thyroid cancer survivors in long term follow up? *Iran J Nucl Med*. 2015;23(1):21-6.
 25. Vuchetich PJ, Garis RI, Jorgensen AM. Evaluation of cost savings to a state Medicaid program following a sertraline tablet-splitting program. *J Am Pharm Assoc*. 2003;43(4):497-502.
 26. Curtiss FR. Tablet splitting to improve the value-for-money equation in cholesterol management. *J Manag Care Pharm*. 2002;8(6):519.
 27. Fawell NG, Cookson TL, Scranton SS. Relationship between tablet splitting and compliance, drug acquisition cost, and patient acceptance. *Am J Health Syst Pharm*. 1999;56(24):2542-5.