

TRABAJO ORIGINAL

Acceleration of the Increase of Endogenous Thyrotropin Hormone for Follow up Studies or Radioiodine Treatment in Patients with Differentiated Thyroid Carcinoma

Incremento rápido de tirotrófina endógena en pacientes con carcinoma diferenciado de tiroides para seguimiento o tratamiento con radioyodo

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Abstract

In follow up (F-U), ablation (A), or treatment (T) with radioiodine of patients with differentiated thyroid carcinoma (DTC), it is necessary to obtain elevated figures of serum TSH to assess hTg serum values or carry out ¹³¹I scanning.

During the past few decades, the method employed was the withdrawal of hormonal treatment (WTH) for several weeks and its variants with the inconvenient symptoms of hypothyroidism, often restraining the use of this method.

We aimed to obtain a rapid rise of serum TSH after a very short withdrawal of thyroid hormonal treatment (eight to nine days) with the use of three or four intravenous application of TRH (200 mcg) during the first 6 days of withdrawal (TRH-St). One hundred determinations were carried out in 66 patients with DTC (ages 19-80 y.o), 20 males and 46 females. Sixty seven TRH-St were carried out for F-U, 20 for FU/T and 13 for A. In all cases the TSH values after the 3rd or 4th TRH application (samples 1 and 2) were over the value of 25 mIU/L and in the case of the second sample 99/100 determination were over the value of 30 mIU/L. The values obtained were for the first sample 70.9 mIU/L ± 54.5 (range 25-310)

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and for the second sample 85.2 ± 61.3 (range 26-360), $p < 0.001$. Patients considered that the symptoms and discomfort observed were mild when compared to those observed in patients submitted previously to the WTH method for 4/5 weeks. The results observed with TRH-St, allow us to consider the method as an alternative to the classic withdrawal method or the use of rhTSH with an adequate relation cost benefit. **Rev Argent Endocrinol Metab 47: 03-13, 2010**

No competing financial interest exist.

Resumen

Para efectuar ablación (A), tratamiento con radioyodo (T) o seguimiento (S) en pacientes portadores de carcinoma diferenciado de tiroides (CDT) se hace necesario incrementar los valores de tirotrófina sérica (TSH) para elevar la sensibilidad del centellograma y la especificidad de la determinación de tiroglobulina sérica (hTg). Por años el método clásico fue la suspensión del tratamiento opoterápico (WTH) o sus variantes y ocasionalmente el uso de TSH de origen animal o, raramente, humana. Hace una década, la introducción de la TRH recombinante (rhTSH) significó evitar la desagradable sintomatología del hipotiroidismo que conllevaba el uso del método (WTH) y que en ocasiones impedía su utilización. Nuestro objetivo: el rápido ascenso de la TSH sérica después de muy breve WTH (ocho a nueve días) utilizando tres o cuatro aplicaciones intravenosas de la hormona liberadora de tirotrófina (TRH) durante los primeros seis días de WTH, método que denominamos TRH-St. Se efectuaron cien TRH-St en 66 pacientes: 20 masculinos, 46 femeninos, edades 19-80 años; 61 carcinomas papilares de diversas variantes anatomopatológicas, 4 foliculares y una variantes Hürthle. En todos los estudios después de la 3ra y cuarta aplicación de TRH (muestras 1 y 2 respectivamente) los valores de TSH fueron superiores a 25 mUI/L y con respecto a la cuarta TRH, 99/100 estudios ofrecieron valores de TSH superiores a 30 mUI/L. Los promedios obtenidos fueron: muestra 1 : $70.9 \pm 54,5$ mUI/L de TSH (rango 25-310); muestra 2: 85.2 ± 61.3 (rango 26-360): $p < 0,001$. Los pacientes consideraron que la sintomatología adversa del hipotiroidismo y el "disconformismo" fueron leves y sin comparación con los observados por aquellos pacientes sometidos anteriormente al método de supresión hormonal por 4/5 semanas.. Estas observaciones nos llevan a considerar que el método TRH-St, es una alternativa válida del método clásico de suspensión hormonal o del uso de rhTSH con una relación adecuada costo / beneficio. **Rev Argent Endocrinol Metab 47: 03-13, 2010**

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Introduction

Post surgical radioiodine ablation (A), periodical follow up (F-U), treatment with radioiodine (T) of remnants, relapses or metastasis and determination of stimulated thyroglobulin serum values (hTg) in patients with differentiated thyroid carcinoma (DTC), need adequate elevated figures of serum thyroid stimulating hormone (thyrotropin - TSH) to increment the sensitivity of whole body scanning (WBS) with radioiodine and the specificity of serum hTg. To accomplish this stop of stimulation of endogenous TSH (En-TSH), withdrawal of thyroid hormone treatment (WTH) for several weeks and its variants for many years

has been the only widely available method, with the subsequent induction of hypothyroidism. Values of serum TSH proposed as adequate for controls are of 25 or 30 mIU/L.⁽¹⁻¹¹⁾

Our objective was to corroborate if the iterative stimulation with thyrotropin releasing hormone (TRH) after thyroid hormonal treatment withdrawal would be able to reach in a short-term adequate levels of endogenous TSH (en-TSH), avoiding or reducing the unpleasant sights and symptoms of hypothyroidism.

Material and methods

Between June 1st 2005 and July 31st 2009,

66 patients with differentiated thyroid cancer (DTC) underwent 100 rapid En-TSH elevation by employing an iterative administration of TRH (TRH-St). Twenty patients were male and 46 female. Age ranged between 19 and 80 years. Etiology of the DTC was in 61 cases papillary carcinoma with different pathologic variations, being 4 were pure follicular type, including in this second group 1 case of Hürthle. The initial surgical treatment was (near-) total thyroidectomy followed by radioiodine ablation^(8,10). Subsequently, l-thyroxine (T4) at individual doses was administrated to obtain TSH plasma values under 0,01 mUI/L in all cases. Only patients with negative anti thyroglobulin antibodies were included. The study was approved by our institution's ethics committee, and written informed consent was obtained from all patients.

The method proposed of iterative TRH stimulation (TRH-St) was as follows:

- 1) T4 withdrawal.
 - 2) Treatment with l-Triiodothyronine (T3) at metabolic equivalent dose, during 3 weeks.
 - 3) T3 withdrawal.
 - 4) Intravenous injection of 200 mcg of TRH (ELEA or Lab. Ferring, C.A Buenos Aires, Argentina, indistinctly) at days 1, 3, 5 and 6 after T3 withdrawal.
 - 5) Thirty minutes after the 3rd injection, a blood sample was obtained for TSH determination and 370 MBq of ^{99m}Tc pertechnetate was administrated i.v ; 60 minutes later a WBS was carried out [12-15] .
 - 6) Thirty minutes after the 4th TRH administration a blood sample was obtained and TSH, hTg and antibody hTg determinations were carried out and then the indicated ¹³¹I activity for F-UP or treatment was administered. The WBS were carried out at 48 hours or at 5 to 7 days⁽⁵⁻⁷⁾
- In 5 patients with previous repeated follow up with hTg positive and negative WBS, 18F-FDG

Table 1 Summary of findings and characteristics of patients

Patients 66		Studies 100		
Male : 20	(Studies 29)	Female: 46 (Studies 71)		
	Mean ± SD	Median (interquartile range)		
Age (y)	49.8 ± 14.9	49.0(36.0-61.8)		
Follicular	5 (5%) including Hürthle			
Papillary	95 (95%) several variations AP			
Objective of the study				
F-U	67 (67%)			
F-U/T	20 (20%)			
A	13 (13%)			
TSH (mUI/L) after				
	Mean (± SD)	Median (IQR)	Range	
3 rd TRH	70.9 ± 54.5	59.2 (35.4-108.1)	25-310	
4 th TRH	85.2 ± 61.3	72.4 (47.8-131.0)	26-360	
Difference	14.3 ± 8.7	p< 0.001		
HTg (ng/ml)	15.3 ± 73.9	0.3 (0.3-5.4)		
WBS	¹³¹I	¹⁸F-FDG	Total	
Negative	74	3	77	
Positive	21	2	23	
F-UP: follow-up; Treatment with ¹³¹I; F-UP/T : follow up and treatment				

Table 2. TSH serum values obtained after the 4th TRH administration in patients that carried out more than one study with TRH-St

Patient	Serum TSH value (UI/L) after 4 th TRH			
	A	1 st F-U	2 nd F-U	3 rd F-U
1	170	64	68	
2	38	43		
3	132	86	92	73
4	130	85		
5	360	190	220	
6	74	60	65	
7	59	73	58	
8	130	158	146	
9		72	86	150
10	180	180	220	
13		40	47	
14		40	94	
15		95	170	
17		36	37	
36	130	114	69	
37		87	118	
39		65	82	
50		97	93	
52		160	160	

A: ablation ; F-U: follow up

was used for Positron emission tomography/ Computer tomography (PET-TC) scan^(16,17) and immediately after the PET/CT study, radioiodine was administrated (shot in the dark).

TRH-St was utilized in 13 patients for ablation. Of these 13 patients , 4 were treated previously to surgery, in periods between 5 months to several years, with thyroid hormone (T4) and they withdrawal the hormonal treatment 3 weeks before surgery. In this group 7-10 days after surgery TRH-St was apply.

The method TRH-St was utilized several times in 19 patients. Table 2 shows the TSH values obtained

after the 4th TRH administration in each of the studies.

The determination of TSH plasma values in 11 studies were carried out also at 24, 48 and/or 72 hours after the 4th administration of TRH (Table 3) All patients were under low iodine regimen during the last 15 days prior to radioactive tracer administration.

Patients were enquired about symptoms after withdrawal of T3 treatment and those patients with previous ablation or follow up in which the protocol utilized was the hormonal withdrawal for several weeks, about the differences observed

Table 3. TSH serum values 24, 48 and/or 72 hours after the 4th administration of TRH in a group of 11 patients, some of them to be treated with ¹³¹I

Patient	Study	TSH serum values (mUI/L) after				
		3 rd TRH	4 th TRH	24 h	48 h	72 h
3	3	103	132	108		
5	47	162	190		126	
3	48	59	73	63	61	
39	49	55	65	60		
47	60	53	66		50	
5	62	185	220	167		
48	64	83	91	80	79	
49	65	40	59	47	41	
50	66	84	97		69	52
51	67	69	81	78		60
52	68	143	160	143		

Results

in relation with the actual protocol.

Hormonal determination was performed using TSH and hTg immunometric electroluminescence (EQLIA) and for hTg -Ab ultra sensitive immunoradiometric (IRMA), respectively.

Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as mean \pm SD⁽¹⁸⁾. The Bland Altman method⁽¹⁹⁾ was applied to evaluate the change in serum TSH after the 3rd and 4th application of TRH according to the mean TSH value. Comparisons among groups were performed using paired samples t-test. A two-sided p value of less than 0.05 indicated statistical significance. Statistical analyses were performed with use of SPSS software, version 13.0 (Chicago, Illinois, USA).

Table 1 depicts demographic and TSH values. In sixty seven studies, TRH-St was utilized for follow-up, and in 20 for hTg and WBS determination previously to treatment with radioiodine. In this second group were included 5 cases with previous studies with positive hTg and negative WBS with radioiodine in which PET/CT were carried out and a therapeutic activity of ¹³¹I was administered; 3 cases show positive results with PET/TC, in local nodes and lung and the other two were negative with both tracer (¹⁸F-FDG and ¹³¹I). In 13 patients TRH-St was employed for ablation

After the 4th TRH administration, the 100 studies showed serum TSH values over 25 mUI/L^(5,23) and ranged between 26 and 360 mIU/L (table 1 and Figures 1 and 2) with a mean value of 85.2 \pm 61.3 mIU/L. Only one patient presented a TSH value of 26 mUI/L, below the previously described 30 mIU/L cutoff⁽¹¹⁾. This patient was

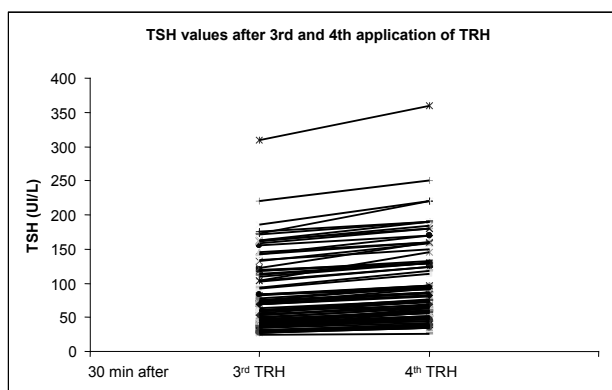


Figure 1

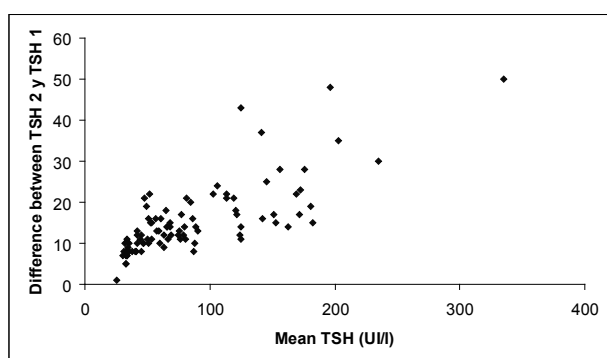


Figure 2. Application of the Bland and Altman method (see text)

under treatment for a depressive syndrome with paroxetine and she only withdrawal such treatment after the first injection of TRH, despite previous recommendation. The mean value of TSH after the 3er TRH was $70.9 \text{ mIU/L} \pm 54.5$ and all were over 25 mIU/L , with only 2 cases under 30 mIU/L , and a range between 25 and 310 mIU/L . In general, age and large periods of l-T₄ treatment were associated with lower TSH values.

In the ablation group, 4 patients were treated prior to surgery with T₄ and showed the lowest figures of TSH. Ten patients of this groups carried out follow up with TRH-St (table 2) and the other 3 since they were treated surgically and carried out ablation recently had no posterior control. One of these patients showed at the first control positive findings on hTG and WBS

determination, with remnants and positive local nodes. He was treated with surgery and therapeutic activity of radioiodine. Other nine patients of this group were found free of illness with negative WBA and hTg.

Nineteen patients carried out more than one TRH-S, including 10 of the group of ablation (table 2). In one patient TRH-St was carried out 4 times, in 7 patient in 3 times and twice in 11 patients, whereas it was utilized once in the rest of the patients.

The Bland-Altman plot (Figure 2) depicts a systematic increase in serial TSH measurements in all patients after 4th application of TRH (sample n^o 2), that is larger in patients with higher basal TSH levels (sample n^o 1). This figure allows to estimate the necessity of the 4th application of TRH or to avoid the same.

Table 3 shows the TSH values in 11 patients obtained between 24 and 72 hours after the last TRH application. Most of them were treated with radioiodine and samples were obtained to determine if TSH levels were adequate to administrate the tracer.

The scans with ¹³¹I and ^{99m}Tc showed similar figures, except two cases that showed in the ¹³¹I WBS with diffuse hepatic uptake, resulting of ¹³¹I-labeled hTg⁽¹⁾.

WBS and serum hTg determinations were negative in 54 studies and were positive in 28 studies. In 28 studies were positive for hTg values (range 1.0 to 680 ng/ml) and negative for WBS; in 8 of these patients with TSH values between 1.0 and 7.0 the decision was to wait and see.

No adverse effects were observed and particularly patients that in previous controls were submitted to HW for several weeks, expressed that the symptoms observed with the TRH-St protocol were mild and tolerable.

Discussion

Our aim was to obtain a rapid increase of En-TSH with TRH stimulation in a very short time frame after withdrawal of hormonal treatment and before carrying out WBS and hTg determination or treatment with radioiodine, minimizing the

undesirable symptoms of hypothyroidism.

During the past few decades, efforts had been made to obtain a method to avoid the symptomatology of hypothyroidism after withdrawal of thyroid hormonal treatment. The use of exogenous TSH of animal origin (beef TSH) has been utilized with the inconvenient production of allergic reactions and antibodies that proscribes the repetition of the method in the same patient ⁽²⁰⁾. The second step was the utilization for a short time of human TSH obtained from necropsies⁽²⁰⁻²²⁾. The real advance was the introduction of recombinant human TSH for ablation, follow up and treatments with radioiodine of remnants, relapses or metastases ⁽²²⁻²⁵⁾.

This method presents a great advantage because patients continue their hormonal treatment and do not present the undesirable symptoms of hypothyroidism. Of course, if patients are treated with T4 they will incorporate high amounts of iodine to the pool of body iodine compartment as a consequence of T4 metabolism and it is recommended by several authors to switch T4 to T3 at equivalent doses for at least 2/3 weeks prior to the study or treatment ⁽²⁶⁻²⁸⁾. In certain occasions such as pituitary insufficiency, cardiac disease, or in patients treated for psychiatric conditions with drugs that suppress the pituitary response to the withdrawal of thyroid hormone treatment, the use of recombinant human TSH is the only possible strategy ⁽²⁹⁾.

It is well known that T3 pituitary inhibition of TSH secretion is less important than T4 inhibition. Several protocols have been introduced switching T4 to T3 at equivalent dose for 2 or 3 weeks and subsequent withdrawal of T3 for additional two weeks [30-31]. More recently, Perez Abdala et al [32] demonstrated that 7 days after switching T4 to T3 for a period of 4 weeks before T3 withdrawal, lead two thirds of patients having TSH stimulated in order to measure hTg or carried out WBS. But in this investigation the T3 doses were not metabolically equivalent to the previous dose of T4; there were sub equivalent. Our secondary objective switching T4 by T3 at metabolic equivalent doses was to obtain adequate levels

of TSH on all the patients through the stimulation with TRH .

TSH pituitary releasing control depends on complex interaction between the stimulating action of TRH and the dose-related negative feed-back of circulating thyroid hormone ⁽³³⁻³⁶⁾.

For decades, TRH was employed for testing thyroid function and in differentiated thyroid cancer as a criterion for the adequacy of TSH suppression hormone therapy ⁽³⁷⁾. In the present study, we used iterative application of TRH to obtain a rapid increase of serum TSH during the first week of withdrawal of T3 hormonal treatment. Consequently, we obtained higher serum TSH values over the limit considered adequate to carry out WBS and hTg determination ^(1-11,23).

In a preliminary report ⁽⁹⁾, we presented the result observed with TRH-St carried out in 37 patients, included in this presentation (group I), and compared the TSH values obtained with those reached in a similar group on patients studied at the same time (group II) employing the WTH method. In group I the mean TSH value was 83 mIU/L \pm 54 and in group II 63 mIU/L \pm 39 ($p = NS$). This observation indicated that the TRH-St method produce the same results as the withdrawal of thyroid hormone treatment for 4/5 weeks.

In Table 2 it can be observed that 10/13 (77%) patients treated with radioiodine after surgery for ablation of thyroid remnants were controlled at least once utilizing the same TRH-St method and the results obtained with the TRH-St method in the follow up allow to consider the efficacy of the proposed method. Except patient number 3 (table 2) that presented thyroid remnants and positive local nodes and was treated with surgery and a therapeutic activity of radioiodine after the first follow up, the other nine were considered free of illness.

As we did not have the possibility of using ¹²³I ⁽³⁸⁾, we employed 99m Tc after the 3rd administration of TRH to obtain a WBS and consider the administration of a therapeutic activity of radioiodine after the 4th TRH.

Magner et al have reported ⁽³⁹⁾ that the TSH obtained after intravenous administration of

TRH is not structurally similar than the basal TRH. Nevertheless, the authors utilized 300 mcg of TRH and they referred also that the TSH of hypothyroid subjects is different than normal TSH. Furthermore, Weintraub and Szkudinski⁽⁴⁰⁾ reported that the recombinant human TSH could not be entirely equivalent to endogenous TSH, indicating that the oligosaccharides are different. However, the four TSH (basal, post-TRH, the one of hypothyroid patients and the rhTSH) stimulated the thyroid cell and produced increment of iodine uptake and secretion of hTg.

In the review of the literature we have found our preliminary presentations^(9,41,42) and two communications of Jara Yor and Lopez Perea^(43,44). These last authors presented different protocols employing one, two or three intravenous application of TRH and different duration of the hormonal withdrawal in the first communication [43], and administration of TRH with two daily doses for 3 days and previous withdrawal of hormonal treatment (T4) for several days⁽⁴⁴⁾.

Going back on time, in 1983 Eissner et al⁽⁴⁵⁾ presented the stimulation of TSH with the oral administration of 40 mg of TRH, with TSH being evaluated 3 hours later. The authors studied 109 patients with DTC and carried out 272 studies obtaining elevated TSH figures, concluding that a recommendation should be issued for TRH stimulation in all patients before diagnostic or therapeutic ¹³¹I application after short T4 withdrawal.

We considered for routine use of TRH-St method only three applications of TRH are needed.

Our observations allow us to consider that the utilization of TRH stimulation to raise TSH in a short term of withdrawal of hormonal treatment provides an alternative to hormone treatment withdrawal for several weeks with the inconvenience of severe hypothyroidism or to the use of rhTSH for patients undergoing ablation, evaluation or treatment with radioiodine of relapses or metastasis of differentiated thyroid carcinoma and presents an adequate cost / benefit relation.

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