IS THERE A DRUG EFFECT ON THE DEVELOPMENT OF PERMANENT HYPOTHYROIDISM IN SUBACUTE THYROIDITIS?

A. Saklamaz*

Izmir Medicalpark Hospital, Dept. of Endocrinology and Metabolism, Izmir, Turkey

Abstract

Context. Subacute thyroiditis (SAT) is a transient inflammatory disease that occurs often after an upper respiratory tract infection. Permanent hypothyroidism ratio is reported in 5-26% of the SAT patients.

Objective. In this study, we tried to compare the treatment options on permanent hypothyroidism in our SAT patients.

Design. It is a retrospective study. The medical records of SAT patients between 2010 and 2015 were analysed.

Subjects and Methods. The medical records of 81 patients were analysed for demographic data, laboratory and clinical course, treatment and 1 year outcome. 81 patients were classified in steroid (n=29), nonsteroidal anti-inflammatory drugs (NSAID) (n=33) and steroid+NSAID (n=19) groups.

Results. Male/female ratio was similar and female domination was demonstrated in all groups. In the steroid and NSAID groups the pretreatment thyroid function tests were diagnosed as hyperthyroidism. In the steroid+NSAID group they were not diagnosed as hyperthyroidism in the beginning. In all groups the thyroid function tests were all in normal levels ($p>0.05$) one year later. In all groups the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were increased in the pretreatment period and decreased with the treatment. In total, right lobe involvement of thyroiditis was more detected (40/81 (49%)) ($p=0.018$). Permanent hypothyroidism observed in steroid, NSAID, and steroid+NSAID groups were 7/29 (24%), 5/33 (15%), 3/19 (16%) respectively ($p>0.05$).

Conclusion. In this study, treatment drug option did not affect the permanent hypothyroidism one year after in our SAT patients.

Key words: subacute thyroiditis, nonsteroidal anti-inflammatory drug, steroid, permanent hypothyroidism.

INTRODUCTION

Subacute thyroiditis (SAT) (de Quervain's granulomatous or giant cell thyroiditis) is a transient

inflammatory thyroid disease that often occurs after an upper respiratory tract infection possibly caused by mumps, coxsackie, influenza, echo and adenoviruses (1, 2). Female dominance is remarkable. Patients most often present with complaints of neck pain and symptoms of hyperthyroidism. In addition, when the elevated erythrocyte sedimentation rate (ESR) and low radioiodine uptake are detected the diagnosis can be made easily. For mild cases nonsteroidal anti-inflammatory drugs (NSAID) are often preferred but for moderate or severe cases glucocorticoids are mostly prescribed (3).

In clinical follow-up with laboratory findings, it is shown that SAT has three clinical phases (4). Initially overt or subclinical hyperthyroidism, the second phase is a transient hypothyroidism in the first-six months and at the final stage (12 months later) euthyroid phase rotation. Following subacute hyperthyroidism, permanent hypothyroidism was reported in 5-26% of the patients (2, 5, 6).

In subacute thyroiditis the effect of clinical presentation, thyroiditis area (measurement of hypoechoic area on the ultrasound view as a volume calculation), and treatment drugs on the development of permanent hypothyroidism have been reported in different papers (5-7). Fatourechi *et al.* reported that more patients who had received corticosteroid therapy had permanent hypothyroidism. The reason for this was suggested that these patients had more severe subacute thyroiditis attack (5). In subsequent publications, the drugs used in the treatment, the size area of thyroiditis and the levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), thyroglobulin (Tg) failed to show a significant effect on permanent hypothyroidism (6, 7).

In this study we retrospectively tried to analyse demographic and clinical features of our SAT patients and to compare the treatment options on permanent hypothyroidism.

*Correspondence to: Ali Saklamaz MD, Izmir Medicalpark Hospital, Dept. of Endocrinology and Metabolism, 1825 sok No:12/2, Yenigirne Karsiyaka, Izmir, 35575, Turkey, E-mail: asaklamaz@hotmail.com

MATERIALS AND METHODS

The patients that had diagnosed subacute thyroiditis in our University Hospital between 2012 and 2014 were retrospectively analysed. The medical records of 81 patients were reviewed for demographic data, laboratory and clinical course, treatment and 1 year outcome. An inclusion criterion for the diagnosis of SAT was painful thyroid gland that was accompanied with either low I131 uptake or increased ESR, or both. Exclusionary conditions were acute exacerbation of chronic thyroiditis, bleeding into a thyroid cyst, acute suppurated thyroiditis and using levothyroxine before the diagnosis.

Laboratory methods

Thyroid stimulating hormone (TSH) (normal range 0.5-4.4 uIU/mL), free thyroxine (FT4) (normal range 0.93-1.7 ng/dL), free tri-iodothyronine (FT3) (normal range 2-4.4 ng/dL), anti-tyroglobin antibodies (Anti-Tg) (normal range < 115 uIU/mL) and anti-thyroid peroxide antibodies (Anti-TPO) (normal range < 34 uIU/mL) concentrations were measured using chemiluminescent micro particle enzyme immunoassay (CMIA) method. Thyroglobulin (Tg) (normal range 2-35 ng/mL) was measured using an electrochemiluminescence immunoassay (ECLIA); C-reactive protein (CRP) (normal range < 0.5 mg/dL) was measured by particle association turbidimetric assay (Cobas Integra 400 plus; Roche Diagnostics, Indianapolis, USA).

Statistical analysis

Statistical analyses were performed using the Rstudio software via R language (version 0.98.501, Wirtschaftsuniversität Wien Welthandelsplatz 1 1020 Vienna, Austria). Continuous variables were reported as mean $\pm$ standard deviation. Categorical variables were reported as number and percent. Normality for continuous variables in groups was determined by the Shapiro Wilk test. The variables showed a normal distribution ($p>0.05$) and Levine test was used to assess the homogeneity of the variances, so One-way ANOVA and Pearson's chi-square test were used to compare the continuous and categorical variables between the groups. When an overall significance was observed after ANOVA, pairwise post-hoc tests were performed using LSD test. For comparison between the pre- and post-treatment data of the treatment group and between the initial data and the data obtained after 1 year later, the paired sample t-test was used for homogeneous

data. A value of $p<0.05$ was considered statistically significant.

The medical ethics committee of our hospital approved the study. The researcher declares that he complied with the ethical principles of the Declaration of Helsinki during this research. The written and informed consent was provided from all patients.

RESULTS

Demographic data

Eighty-one patients were classified in 3 groups. The only steroid or NSAIDs given groups had 29 and 33 patients respectively. The group that was prescribed both NSAID and steroid had 19 patients. There was no statistical difference in the mean ages of the groups ($p>0.05$). The male/female ratios were 6/23, 8/25, 5/14 in steroid, NSAID, and steroid+NSAID given groups respectively ($p>0.05$). Male/female ratio was similar and female domination was demonstrated in all groups (Table 1).

Laboratory data

The laboratory data at the admission and one year later are shown in Table 1. In the steroid and NSAID groups the pre-treatment thyroid function tests were diagnosed as hyperthyroidism. In the steroid+NSAID group they were not diagnosed as hyperthyroidism in the beginning but the TSH values were significantly different from the NSAID groups' TSH values ($p<0.05$). There were also significant differences in the FT4 levels of the steroid and steroid+NSAID groups ($p<0.05$). In all groups the thyroid function tests were all in normal levels and there were no differences ($p>0.05$) one year later. The Tg and Anti-Tg levels were increased in all groups at the SAT diagnosis, and one year after the diagnosis the levels of these parameters decreased in all groups ($p>0.05$). Anti-TPO levels were not increased and there were no statistical differences between the groups ($p>0.05$). In all groups the ESR and CRP levels were increased in the pre-treatment period and decreased with the treatment. The pre-treatment ESR levels of steroid+NSAID group were lower than of the other groups ($p<0.05$). One year after the treatment the ESR levels of steroid+NSAID group were significantly lower than of the NSAID group ($p<0.05$). In the beginning the CRP levels of the three groups were increased and one year later the levels were decreased. There were no statistical differences between the groups ($p>0.05$) (Table 1).

Table 1. Demographic and laboratory parameters of patients (before and one year later) (NS: nonsignificant)

	STEROID (n=29)		NSAID (n=33)		STEROID + NSAID (n=19)		p
Age (years)	43.2±11.3		41.6±10.7		39.4±9.4		NS
Male/Female	6/23		8/25		5/14		NS
(Reference values)	Pre-treatment	1 year later	Pre-treatment	1 year later	Pre-treatment	1 year later	
TSH (0.5-4.4 uIU/mL)	0.4±1.0	2.8±2.8	0.32±0.6*	2.3±4.3	2.6±4.4*	3.3±2.6	*<0.05
FT3 (2-4.4 ng/dL)	6.5±3.3	2.8±0.6	6.0±3.5	2.9±0.5	5.1±2.7	2.8±0.5	NS
FT4 (0.93-1.7 ng/dL)	2.8±1.3*	1.1±0.4	2.4±1.3	1.2±0.3	2.0±1.4*	1.1±0.2	*<0.05
Anti-Tg (< 115 uIU/mL)	151±269.8	133±218.1	160±237.7	99±157.1	153.4±221.4	75±119.8	NS
Anti-TPO (< 34 uIU/mL)	11±5.6	9.2±5	22.3±33.9	37.5±68.9	19.4±18.6	15.4±16.5	NS
Thyroglobulin (ng/dL)	471±899	120±238	259.6±233.8	40±31	105.8±73.4	62.4±62.6	NS
ESR (< 20 mm/h)	43.3±15.7*	13.2±7.4	47.9±23.1 [‡]	16±17.5 [§]	24.9±17.5* [‡]	6.6±2.9 [§]	[‡] * [§] <0.05
CRP (< 0.5 mg/l)	5.9±3.7	0.7±0.7	15.9±46.7	0.7±1	3.2±3.2	0.5±0.8	NS

In the TSH row; * the significant difference was found only in the pre-treatment TSH levels between NSAID and Steroid + NSAID groups (gray coded).

In the FT4 row; * the significant difference was found only in pre-treatment FT4 levels between Steroid and steroid+NSAID groups (gray coded).

In the ESR row; * the significant difference was found in pre-treatment ESR levels between steroid+NSAID and Steroid groups (gray coded).

[‡] the significant difference was also found in pre-treatment ESR levels between steroid+NSAID and NSAID groups (gray coded).

[§] the significant difference was found 1 year later in ESR levels between steroid+NSAID and NSAID groups.

Side of thyroiditis involvement

The involvement side of subacute thyroiditis is checked from the patients' examination records. The most of the patients in only steroid used group had thyroiditis in the right lobe (21/29 (72.4%)). Diffuse and right lobe involvement sides were equal and more than the left lobe involvement in the steroid+NSAID used group (8/19 (42.1%)). The only NSAID used group had equal number of patient numbers in all sides of thyroiditis involvement (right, left, diffuse 11/33, (33.3%)). The right lobe involvement side of thyroiditis (40/81 (49%)) was more detected than the diffuse and left side involvement (21/81 (26%), 20/81 (25%) respectively) in total (p=0.018) (Table 2).

Permanent hypothyroidism

Permanent hypothyroidism observed in steroid, NSAID, and steroid+NSAID groups were 7/29 (24%), 5/33 (15%), 3/19 (16%) respectively (p>0.05) (Table 3).

No correlation was found between the patients initial examination findings (sedimentation, CRP, thyroid antibodies, TSH, FT4, FT3 levels and thyroiditis side) and permanent hypothyroidism (data not shown).

DISCUSSION

Subacute thyroiditis develops after a viral infection. But we know that subsequently occurring events of the immune system play a role in the series. Meanwhile the cytokines, that are secreted by the cell-mediated immunity against thyroid glands, cause thyroid pain (8, 9). In this case, there are corticosteroids and NSAID as a treatment option in our hands.

In our patients, treatment drug option did not affect the permanent hypothyroidism one year after the first examination. But in steroid used group, more patients had thyroid replacement therapy than the other groups (p>0.05). The clinical outcome of SAT patients according to the treatment drug options was reported in few reports (5-7). Fatourechi *et al.* reported that in the long term follow-up the steroid used group had more permanent hypothyroidism, and this may be because of the severity of the SAT attack (5). But in the paper they did not classify the severity of SAT by ESR, CRP, Anti Tg, Tg levels according to the drugs prescribed. Benbassat *et al.* classified fifty-six SAT patients and reported that although glucocorticoid used

Table 2. Showing the side of pain and number of patients who had pain in the neck at the examination by the doctor (side of thyroiditis involvement) (*p<0.05) (NS: nonsignificant)

	Diffuse (n)	Right Lobe (n)	Left Lobe (n)	Total (n)	p
Steroid	2 (6.9%)	21 (72.4%)	6 (20.7%)	29 (36%)	NS
NSAID	11 (33.3%)	11 (33.3%)	11 (33.3%)	33 (41%)	NS
Steroid+NSAID	8 (42.1%)	8 (42.1%)	3 (15.8%)	19 (24%)	NS
Total	21 (26%)*	40 (49%)*	20 (25%)*	81 (100%)	0.018

Table 3. Permanent hypothyroidism in the groups (p>0.05) (NS: nonsignificant)

	Steroid	NSAID	Steroid+NSAID	p
Hypothyroidism	7/29 (24%)	5/33 (15%)	3/19 (16%)	NS

group had more severe clinical features, there was no difference between the NSAID used group in developing permanent hypothyroidism (10). In a retrospective study Omori *et al.* reported that hypoechoic areas reflected the inflammation of the thyroid (so the severity of SAT) and the size of them were correlated with the blood Tg and Anti Tg levels (11). But these images was not correlated with the hypothyroidism in the outcome. In another study, Schenke *et al.* reviewed the records of 72 patients who had subacute thyroiditis (6). They reported that there was no predictive factor for the thyroid hormone replacement therapy but the thyroid volume values were lower in the replacement taken group (6). Cappelli *et al.* evaluated 22 SAT patients by clinical, sonographic features, and laboratory findings (12). They prescribed 25 mg prednisone to all patients for 10 weeks with tapered doses by 5 mg/2 weeks. In multiple regression analysis, the delay in the starting time of the prednisone therapy was reported to be related to the occurrence of permanent hypothyroidism. (12) ($p < 0.05$). Any of age, gender, thyroid volume, and bilateral subacute thyroiditis side did not affect the hypothyroidism in the follow-up (12).

In our patients the severity of the SAT was not calculated in the first examination. Only pain and the side of the thyroiditis were recorded in the patients' files. If we try to estimate the severity of the SAT according levels of laboratory tests in the first visit, the NSAID group had much higher levels of ESR, CRP, and Anti-Tg levels. But the steroid given group had higher levels of Tg and FT4 levels. Benbassat *et al.* scored the severity of SAT patients according to the clinical features: fever, tenderness, goitre by ultrasonography or palpation, and ESR levels. And they reported that there were no correlations between the clinical scores, ESR and peak FT4 or maximal TSH levels (10). In another report the hypoechoic area on the ultrasonography of the SAT patients correlated well with the neck pain, serum FT4, and Anti-Tg levels (11). We could not get all of our patients' thyroid ultrasound reports and pictures, so the thyroiditis area could not be measured in our study.

In our study female dominance is remarkable (male/female, 19/62) and seems compatible with the literature. In the literature male/female ratio is reported from 1:2 to 1:10 (2, 13-15). In our patients this ratio is 1:3.

Thyroiditis side data were compiled according to the report of the physical examination of patient records. Right lobe involvement was found to be significantly higher in total (40/81, 49%). The ratio of the first attack side in the thyroid gland in patients with SAT is not found in literature.

Our study has some limitations. Firstly, this is a retrospective study so diagnostic tests and treatment drugs, doses are not homogeneous for all patients. Second, we could not reach the reports of thyroid ultrasonography for most of patients, so these could not be taken into consideration.

In conclusion, we could not find a drug effect on the permanent hypothyroidism in subacute thyroiditis.

Conflict of interest

The author declares that there is no conflict of interest to disclose.

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