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ORIGINAL ARTICLE

Comparison of the therapeutic effects of prednisolone and nonsteroidal anti-inflammatory drugs in patients with subacute thyroiditis

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Abstract Subacute thyroiditis is a transient inflammatory thyroid disease of unknown etiology. The primary goal for treatment is to mitigate inflammation. The aim of this retrospective study was to compare the therapeutic effects of prednisolone and nonsteroidal anti-inflammation drugs in patients with subacute thyroiditis. In this study, 53 consecutive Japanese patients who had been diagnosed with were referred to our hospital for further management. After excluding 11 patients (9 did not need treatment, 2 did not meet the criteria for diagnosis of subacute thyroiditis), the remaining 42 patients were treated either with prednisolone ($n = 25$) or loxoprofen ($n = 17$). We compared the time periods required for resolution of clinical symptoms and signs and normalization of thyroid function between the two groups. The mean dose of prednisolone was 15.0 (range, 14–16) mg/day and that of loxoprofen was 180 mg/day. The time period to normalization of thyroid function was comparable between the prednisolone and loxoprofen groups (25, 18–36, vs 32, 21–39 days, $p = 0.388$). However, the time period for resolution of symptoms was shorter under prednisolone than loxoprofen (7, 7–12 days, vs 21, 14–32 days, $p < 0.001$). Prednisolone treatment of patients with subacute thyroiditis was superior to nonsteroidal anti-inflammation drugs with regard to resolution of symptoms.

Keywords Subacute thyroiditis · Glucocorticoid · Nonsteroidal anti-inflammatory drugs · Therapeutic effectiveness

Abbreviations

eTV	estimated thyroid volume
FT3	free triiodothyronine
FT4	free thyroxine
NSAIDs	nonsteroidal anti-inflammatory drugs
PSL	prednisolone
SAT	subacute thyroiditis
STA-PSV	mean peak systolic velocity of superior thyroid artery
TRAb	thyrotropin receptor antibody
TSH	thyrotropin

Introduction

Subacute thyroiditis (SAT) is a transient inflammatory thyroid disease of unknown etiology. The prevalence of SAT is about 5 % among thyroid abnormalities [1]. The main symptoms of SAT are related to the inflammatory reaction, and include high fever and front neck pain with tenderness, resembling common cold or upper respiratory tract infection. The primary aim of treatment of SAT is to mitigate inflammation by anti-inflammatory agents such as glucocorticoid, nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates. According to the clinical guideline of the American Thyroid Association, the selection of anti-inflammatory agents should be based on the severity of symptoms; NSAIDs and salicylates for patients with mild

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symptoms and glucocorticoids for those with moderate-to-severe symptoms [1–3]. To our knowledge, there is little or no information on the differences in the therapeutic effectiveness of various anti-inflammatory agents used for the treatment of patients with SAT. The aim of the present retrospective study was to compare the therapeutic effectiveness of glucocorticoids and NSAIDs in patients with SAT.

Patients and methods

Patients

This is a retrospective observation study involving 53 consecutive Japanese patients (12 males, 41 females) who were diagnosed with SAT based on the clinical guidelines of the Japan Thyroid Association (http://japanthyroid.jp/doctor/guideline/english.html) between 2008–2014 at the Diabetes and Endocrine Clinics of Juntendo University Hospital. Of the 53 patients, 49 (92.2 %) were referred from other clinics and 19 out of the 49 patients visited more than two clinics before they visited our hospital. The initial diagnosis by the referring physicians were SAT ($n = 29$ patients, 61.9 %); thyroid functional abnormalities ($n = 16$, 21.4 %); goiter ($n = 5$, 4.8 %); and uncertain ($n = 6$, 14.3 %). Among them, three patients were diagnosed with goiter and functional thyroid abnormalities. The anti-inflammatory drugs selected by referring physicians included acetaminophens ($n = 25$ patients, 47.2 %); NSAIDs ($n = 28$, 52.8 %) (Supplementary Table 1). The baseline characteristics of patients except age (gender, mean interval between onset and first visit to our clinic, clinical symptoms, results of laboratory test and thyroid ultrasound findings) at first visit to our clinic of the acetaminophen-treated group and NSAIDs-treated group were statistically similar (Supplementary Table 1). The study protocol was approved by the ethics committee of Juntendo University.

Measurement of serological makers

Blood samples were collected from all patients. Free thyroxine (FT4), free triiodothyronine (FT3), and thyrotropin (TSH) values were measured using a commercial electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo; FT4: normal range, 1.00–1.70 ng/dL; FT3: normal range, 2.40–4.50 pg/mL; TSH: normal range, 0.56–4.30 μIU/mL). Serum TSH receptor antibody (TRAb) was measured using a two-step radioreceptor assay DYNO test TRAb (Yamasa Corp, Tokyo; normal range, <1.0 IU/L; detectable level, ≥1.0 IU/L) or another two-step radioreceptor assay ECLusys TRAb (Roche Diagnostics, Tokyo; normal range, <2.0 IU/L; detectable level, ≥ 0.3 IU/L). Thyroid autoantibodies [thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb)] were measured using a radioimmunoassay (Cosmic Corp, Tokyo). Thyroglobulin (Tg) value was measured using a commercial electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo; Tg: normal range, ≤32.7 ng/mL).

Ultrasonography

The mean superior thyroid artery peak systolic velocity (STA-PSV) and estimated thyroid volume (eTV) were measured in all subjects by two expert ultrasonographers using a 12.0-MHz linear transducer of the LOGIQ P6 ultrasound (GE Healthcare) as described in detail previously [4]. Briefly, the mean STA-PSV was measured based on the Doppler spectrum time-averaged mean velocity and the vessel diameter, with the angle between the ultrasound beam and vessel axis kept at ≤60°. The eTV was computed using the ellipsoid model [(width × length × thickness × π/6) for each lobe + (width × length × thickness) for the isthmus].

Treatment

There are no guidelines for the selection of glucocorticoids (prednisolone, PSL) and NSAIDs (loxoprofen) for the treatment of patients with SAT. Thus, the drug selected and dose were based on the clinical experience of the attending endocrinologists. PSL was tapered in 5 mg steps from the initial dose biweekly in most patients (76 %) and weekly in the other patients (24 %). In all patients on NSAIDs, treatment was discontinued with resolution of symptoms. The resolution of the initial symptoms and thyroid dysfunction were defined as disappearance of subjective symptoms and normalization of thyroid hormones data, respectively.

Statistical analysis

Results are presented as mean ± standard deviation (SD) for parameters with normal distribution, and median with interquartile range (IQR) for those with skewed distribution. Differences in physical signs and various thyroid parameters between PSL and NSAID groups were examined for statistical significance using the student's *t*-test or Mann–Whitney *U*-test, as appropriate. The time taken for the disappearance of initial symptoms and for normalization of thyroid dysfunction between PSL and NSAID groups were compared using the Mann–Whitney *U*-test, and the analysis of co-variance was used to take into account potential differences in patients' characteristics. Categorical data were reported as frequencies and compared using the χ^2test or Fisher's exact test. A p value of <0.05 was considered statistically significant. All statistical analyses were

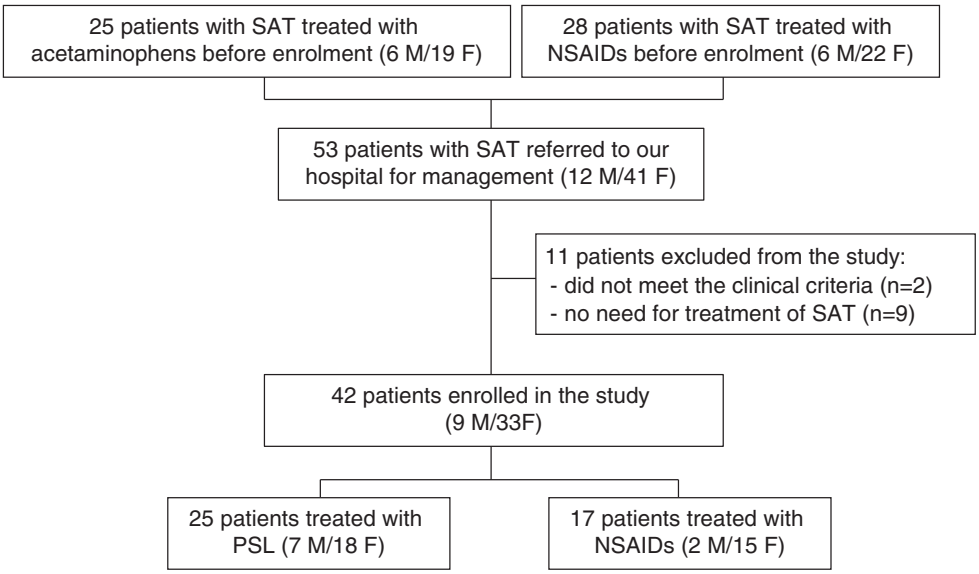

Fig. 1 Patients' selection process. NSIADs used before enrolment included salicylates and acetaminophens. *NSAIDs*: nonsteroidal anti-inflammatory drugs, *PSL*: prednisolone

performed using the statistical package for social sciences (SPSS, Inc., Chicago, IL).

Results

Baseline characteristics

Among the 53 consecutive patients with suspected SAT who visited our clinic, 25 patients were treated with PSL (PSL group) and 17 patients with NSAIDs (NSAIDs group) on the first visit (Fig. 1). The remaining 11 patients did not meet the clinical guidelines of SAT or did not need further treatment. The initial mean dose of PSL was 15.0 (range, 14–16) mg/day. The only NSAID used in this cohort was loxoprofen at 180 mg/day. The baseline characteristics of patients of the two groups (gender, age, symptoms, laboratory findings and thyroid ultrasound findings) at first visit of our clinic were similar (Table 1). In particular, the mean time between onset and first visit to our clinic tended to be shorter in NSAIDs group (14, 14–28 days) than in PSL group (21, 14–28 days, $p = 0.820$, Fig. 2), but the difference was not statistically significant. The time taken for normalization of thyroid dysfunction was similar in the PSL (25, 18–36 days) and NSAIDs groups (32, 21–39 days, $p = 0.388$, Fig. 3). On the other hand, the time taken for the disappearance of initial symptoms was significantly shorter in PSL group (7, 7–12 days) than the NSAIDs group (21, 14–32 days, $p < 0.001$, Fig. 3). In addition, to take into account potential differences in the time between onset and first visit to our clinic, the analysis of co-variance adjusting the time between onset and first visit to our clinic was performed. The analysis revealed that the time taken for the disappearance of the initial symptoms was significantly shorter in PSL group than NSAIDs group ($p = 0.002$). The mean follow-up period was almost identical for the PSL and NSAIDs (First to second visit: 15.5 ± 4.1 vs. 15.3 ± 9.0 days, respectively, $p = 0.924$, second to third visit: 24.2 ± 9.3 vs. 21.3 ± 7.8 days, respectively, $p = 0.303$ Supplementary Table 2). The earlier recovery from symptoms in patients treated with PSL did not depend on the difference in the follow-up period.

With regard to the side effects of the two classes of drugs, one patient of the PSL group who had type 2 diabetes mellitus showed clinically significant deterioration of blood glucose control during the treatment. Three patients treated with PSL and one patient with NSAIDs showed recurrence of SAT within 2 months after discontinuation of the drugs, however, there was no significant difference in the recurrence rate between the two groups ($p = 0.635$).

Discussion

The present study encompassed patients with suspected SAT who were previously managed by non-endocrinologists who required further treatment and was designed to compare the effects of PSL and NSAIDs. While the severity of SAT was comparable between the PSL and NSAIDs groups, our data indicate that the time elapsed until resolution of symptoms (rather than normalization of thyroid hormone levels) was significantly shorter in the PSL group than the NSAIDs group.

The baseline clinical characteristics of the 53 patients with SAT were similar to those of patients included in other Japanese clinics, except for thyroid hormone levels [5, 6]. The thyroid hormone levels were higher in our patients with SAT than patients with SAT in other Japanese clinics [5, 6]

Table 1 Characteristics of patients with SAT at first visit to the Diabetes and Endocrine Clinics of Juntendo University Hospital

	Total	PSL	NSAIDs	*p*
Number	42	25	17	
Gender (Male/Female)	9/33	7/18	2/15	0.192
Age (years)	48.8 ± 12.8	47.3 ± 13.8	51.1 ± 11.1	0.345
Symptoms				
Fever (°C)	37.7 ± 0.7	37.7 ± 0.8	37.6 ± 0.7	0.563
Palpitation (+/–)	10/32	5/20	5/12	0.366
Neck pain (+/–)	42/0	25/0	17/0	n/a
Tremor (+/–)	4/38	2/23	2/15	0.538
Hyperidrosis (+/–)	13/29	6/19	7/10	0.237
Weight loss (+/–)	15/27	10/15	5/12	0.482
Diarrhea (+/–)	3/39	2/23	1/16	0.645
Menstrual disturbance (+/–)	2/40	1/24	1/16	0.652
Leg edema (+/–)	3/39	1/24	2/15	0.355
Laboratory findings				
TSH (μU/mL)	0.01 (0.01–0.02)	0.01 (0.01–0.02)	0.01 (0.01–0.01)	0.206
FT3 (pg/mL)	10.1 ± 4.7	10.1 ± 5.0	10.1 ± 4.4	0.98
FT4 (ng/dl)	4.0 ± 1.7	4.0 ± 1.8	4.0 ± 1.6	0.98
FT3/FT4 ratio	2.44 (2.24–2.75)	2.50 (2.32–2.76)	2.35 (2.23–2.71)	0.847
Thyroglobulin (ng/dl)	296 (137–601)	305 (137–464)	282 (238–618)	0.947
TRAb (+/–)	0/42	0/25	0/17	n/a
TPOAb (+/–)	16/26	9/16	7/10	0.735
TgAb (+/–)	19/23	10/15	9/8	0.408
Blood cell count at onset (/mL)				
Total leukocytes	7505 ± 2053	7596 ± 1811	7371 ± 2419	0.732
Neutrophils	5454 ± 1954	5452 ± 1855	5458 ± 2170	0.993
Lymphocytes	1401 (1295–1586)	1403 (1316–1621)	1352 (1295–1592)	0.175
Monocytes	513 ± 174	526 ± 141	493 ± 220	0.576
Eosinophils	79 (40–115)	82 (36–110)	98 (42–114)	0.248
Basophils	12 (9–30)	11 (9–21)	16 (10–32)	0.194
CRP (mg/dl)	3.9 ± 2.7	4.5 ± 2.7	2.9 ± 2.6	0.051
Ultrasound findings				
eTV (g)	24.0 (19.8–35.0)	24.1 (19.8–38.4)	24.0 (21.5–34.5)	0.575
STA-PSV (cm/s)	26.9 (23.0–36.0)	25.6 (22.5–29.7)	28.6 (24.7–38.3)	0.139

Data are mean ± SD, median (IQR) or number of patients

NSAIDs: nonsteroidal anti-inflammatory drugs, *PSL*: prednisolone

but similar to those of other countries [7]. The majority of patients included in this study were referred to our hospital from other clinics, thus it is possible that only patients with severe destructive thyroiditis were selected for referral.

PSL is recommended for patients with severe destructive thyroiditis although the clinical judgment of severity seems to have been based on subjective and objective symptoms. However, there was no significant difference in the clinical background between patients of the PSL and NSAIDs groups, and accordingly cannot find the basis for the selection of treatment. These findings suggest a possible gap between the factors that we pick up and symptoms of SAT. Accordingly, it is possible that PSL was used for patients with more severe SAT. Interestingly, PSL use was associated with a shorter time to the disappearance of initial symptoms. In any case, our data support the notion that PSL treatment is superior to NSAIDs in terms of resolution of symptoms.

The clinical guidelines of the American Thyroid Association recommend 40 mg/day of PSL for the treatment of SAT, which according to the guidelines, can improve the initial symptoms within 72 h [1, 8]. In addition, comparison of the therapeutic effects of 30 mg/day of PSL and 3 g/day of acetylsalicylate (aspirin) showed that PSL was superior

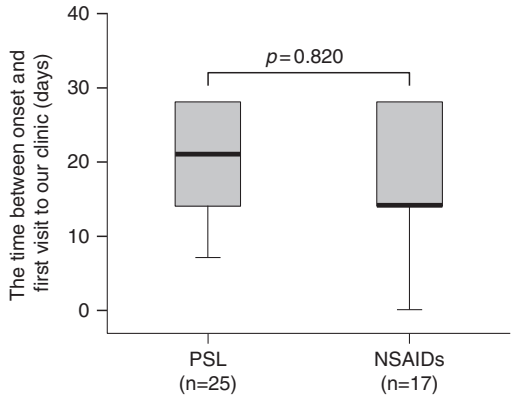

Fig. 2 Comparison of the time between onset and first visit to our clinic between PSL and NSAID groups. Boxplots showed quartiles, median (*bold back lines*) of the time between onset and first visit to our clinic. *NSAIDs*: nonsteroidal anti-inflammatory drugs, *PSL*: prednisolone

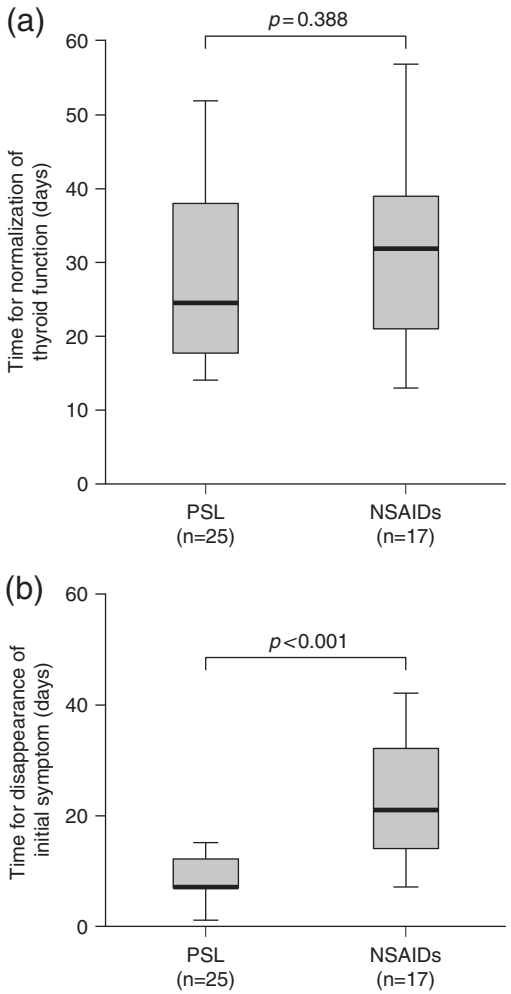

Fig. 3 Comparison of the time taken for the disappearance of the initial symptoms and for normalization of the thyroid function between the PSL and NSAID groups. Boxplots showed quartiles, median (*bold back lines*) of **a** the time taken for normalization of the thyroid dysfunction and **b** the time taken for disappearance of the initial symptoms. *NSAIDs*: nonsteroidal anti-inflammatory drugs, *PSL*: prednisolone

to salicylates in shortening not only the time to resolution of symptoms, but also the time to normalization of thyroid function [2]. These data suggest PSL is more effective in the treatment of SAT-related symptoms than NSAIDs. Our results also showed a better treatment outcome for PSL with regard to SAT-related symptoms, even when used at a dose of 15 mg. From the viewpoint of the dose-dependent adverse effects and the therapeutic effectiveness in relieving inflammatory response, a recent study demonstrated that 15 mg/day of PSL may be sufficient for the treatment of the common forms of SAT [6]. Indeed, in our study, we found no critical adverse effects and the recurrence rate was similar in the two groups. However, in the present study, the mean time period to recovery from initial symptoms by 15 mg/day of PSL was 7 days, which was longer than that of a higher dose of PSL used previously [1, 6]. Thus, with regard to the resolution of symptoms, 15 mg/day of PSL does not seem to be sufficient.

Several factors can affect the time period required for normalization of thyroid functions and disappearance of initial symptoms in patients treated with PSL. First, the treatment used before referral to our clinic could be one such factor. However, in 25 patients treated with PSL, the time periods required for normalization of thyroid functions and disappearance of initial symptoms were comparable between patients pre-treated with acetaminophens ($n = 11$) and NSAIDs ($n = 14$) (7 days, 6–8, vs 8, 7–15) days; $p = 0.870$, 21, 18–32, vs 28, 18–43 days, $p = 0.581$), suggest minimal effect for the pretreatment.

The anti-inflammatory effect of PSL is superior to that of acetylsalicylate or NSAIDs due to the wide-range suppressive effect on chemical mediators [9]. Yamamoto et al. [3] compared the therapeutic effects of 30 mg/day of PSL and 2 g/day of acetylsalicylate in a small-scale study and found that PSL shortened the time period to normalization of elevated Tg levels compared to acetylsalicylate irrespective of the similar recovery period of thyroid dysfunction. Their results could reflect differences in the effects of each treatment modality on local inflammation in the thyroid gland. It is noteworthy that the anti-inflammatory effects of PSL and others did not alter thyroid hormone levels, as shown in our study.

The present study had several limitations. First, this study was small, single-center, retrospective in nature and reflected daily clinical practice. Second, the patients were not randomly assigned to the PSL or NSAIDs groups. However, there was no significant difference in the clinical background between the two treatment groups.

In conclusion, our study demonstrated the superiority of PSL at a dose smaller than that used in previous studies in patients with SAT compared with NSAIDs in the resolution of initial symptoms, rather than normalization of thyroid function.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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