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Efficacy of two different dosages of prednisone for treatment of subacute thyroiditis: a single-centre, prospective, randomized, open-label, non-inferiority trial

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Abstract

Introduction: The study aimed to explore the efficacy and safety of low-dose (LD) and regular-dose (RD) prednisone (PDN) for the treatment of subacute thyroiditis (SAT).

Material and methods: Patients were randomly allocated using the block randomization method to the 2 groups. The primary outcome was the time required for PDN treatment. Secondary outcomes included percentages of relapse, mean score for the Morisky Medication Adherence Scale-8© (MMAS-8), time required for symptoms to resolve, cumulative PDN dose (mg), and mean erythrocyte sedimentation rate (ESR) at 2 weeks and at baseline.

Results: The study cohort included 77 patients, randomized 74 participants, and 68 completed the study. There was no significant difference in the treatment duration between the LD and RD groups (55.31 ± 14.05 *vs.* 61.25 ± 19.95 days, p = 0.053). The mean difference in the time required for PDN treatment between the LD and RD groups was –1.86 [95% confidence interval (CI) = –10.64 to 6.92] days, which was within the non-inferiority margin of 7 days. There was a significant difference in the mean score for MMAS-8 between the LD and RD groups (5.84 ± 0.88 *vs.* 5.33 ± 1.12, p = 0.031). Also, there was a significant difference in the cumulative PDN dose between the LD and RD groups (504.22 ± 236.86 *vs.* 1002.28 ± 309.86, p = 0.046). The ESR at 2 weeks was statistically significant compared to baseline values in both groups, with pre-treatment and post-treatment ESRs of 49.91 ± 24.95 and 17.97 ± 12.60/mm/h, (p < 0.0001) in the LD group and 65.08 ± 21.77 and 17.23 ± 13.61/mm/h (p < 0.0001) in the RD group.

Conclusion: Low-dose PDN therapy may be sufficient to achieve complete recovery and better outcomes for SAT. This study is registered with the Chinese Clinical Trial Registry (02/10/2021 ChiCTR2100051762). **(Endokrynol Pol 2023; 74 (2): 168–175)**

Key words: *subacute thyroiditis; SAT; low dose; prednisone; non-inferiority*

Introduction

Subacute thyroiditis (SAT), also known as De Quervain's thyroiditis, is the most common type of painful thyroid disorder [1–3]. SAT affects people between the ages of 30 and 50 years [2–5], and its incidence is disproportionately higher in women. However, the pathogenesis has not yet been fully elucidated.

Currently, non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat mild cases of SAT, whereas short-term steroid therapy is occasionally used to treat moderate to severe cases, which are characterized by recurrent neck pain, tenderness, and considerable goitre. Prednisone (PDN) is a synthetic corticosteroid commonly used for the treatment of SAT [4, 6]. The 2016 American Thyroid Association (ATA) guideline [4] recommends PDN for the treatment of moderate to severe cases of SAT. The recommended steroid regimen includes PDN at 40 mg/day for 1–2 weeks with gradual tapering of the dosage for 2–4 weeks depending on the clinical response. The 2016 ATA guideline referred to another study with a lower initial dose of 15 mg prednisolone [7], but only for patients in Japan. We hope that the dosage of 15 mg PSL can also be used in China. Therefore, the aim of this non-inferiority study was to explore the clinical efficacy and safety of low-dose (LD) prednisolone (PDN)

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at 15 mg one time per day as compared to the regular dose (RD) at 10 mg 3 times per day for treatment of SAT.

Material and methods

Study design

We performed a prospective, randomized, open-label, single-centre, parallel-group controlled, non-inferiority study in the First Affiliated Hospital of Wannan Medical College (Yijishan Hospital) from 1 Dec 2020 to 30 Dec 2021. All patients provided written informed consent and confirmed their willingness to participate. The protocol was approved by the Institutional Review Board of the First Affiliated Hospital (Yijishan hospital) of Wannan Medical College and was implemented in accordance with provisions of the Declaration of Helsinki. Each patient provided written informed consent before beginning the study procedure.

Participants

Participants diagnosed with SAT were evaluated in terms of eligibility for inclusion in the study. Clinical characteristics, physical exam, radioactive iodine absorption, and laboratory test results — including high erythrocyte sedimentation rate (ESR), serum free-thyroxine (fT4), and free triiodothyronine (fT3) levels with suppressed thyroid-stimulating hormone (TSH) levels — were used to make the diagnosis of SAT. The diagnosis and resolution of SAT were confirmed by thyroid ultrasonography in all patients. In this study, patients with side effects of steroids and pregnancy were excluded.

Randomization and blinding

We randomly assigned patients to 1 of the 2 groups in a 1:1 ratio using a random block with stratification (http://www.randomization.com). A study coordinator was only involved in randomization and allocation. Randomized numbers were sealed in opaque envelopes in order and kept them concealed until the study day. The investigator made a phone call to the study coordinator the day before patient enrolment to confirm the patient's assignment. Assessment of study outcomes was analysed by the investigator. The purpose of this study was to explore the efficacy and safety of different doses of PDN for the treatment of SAT, and complete blinding would not be meaningful for either the investigators or the patients. Therefore, this study was conducted as an open-label study in which only laboratory personnel were blinded, and no randomization groups were allowed to be removed.

Procedures

The dose tapering protocol was 15–10–5–2.5 and 30–20–15–10–5 mg per week for the LD and RD groups, respectively. Treatment duration was extended by 1 or 2 weeks with the continuation of the same dose in the previous week in patients who complained of having increased pain during the dose tapering. The dose was reduced from the week of normalized ESR (about 7–14 days), and the first reduction was 1/3 of the dose. Based on clinical experience and examination results, most patients experienced a complete disappearance of pain within 5–10 days after PDN treatment, either at the small initial dose or at the regular initial dose. Therefore, if patients experienced a recurrence of symptoms during the dose reduction, we adjusted them to the regular initial dose.

After the patients were enrolled, we conducted weekly face-to-face or telephone follow-up visits. The results of the follow-up visits were recorded on the patient's informed consent forms. Each participant received a final visit before the completion of the trial.

Outcomes

The primary outcome of the study was to assess the time (days) required for PDN treatment. The secondary outcomes were as follows: (I) percentages of participants experiencing relapse during and after treatment; (II) the mean score for the Morisky Medication Adherence Scale-8© (MMAS-8); (III) the time (days) required for symptoms to resolve; (IV) the cumulative PDN dose (mg); and (V) the mean ESR at 2 weeks and at baseline.

Safety outcomes included the occurrence of all adverse drug events, which were elevated blood pressure, elevated blood glucose, mood swings, facial acne, insomnia, weight gain, hypothyroidism, etc.

Statistical analysis

Primary and secondary outcomes were analysed based on the full analysis set, with missing values carried forward using the last observation and supportive sensitivity analysis using the last follow-up. Safety outcomes were analysed based on the safety data set, including the set of all subjects who received at least one treatment after randomization. All outcomes were also analysed according to each protocol set. The primary outcome was the time (days) required for PDN treatment. The purpose of this study was to show that low-dose PDN therapy may be sufficient to achieve complete recovery and better outcomes in SAT. Therefore, we hypothesized that the patients randomized to the LD group are non-inferior to the patients randomized to the RD group. To assess for non-inferiority, the non-inferiority delta (Δ) of 7 (days) was chosen for the following reasons. In previous studies [6, 7], the mean time was around 36 days with a standard deviation of 12 days. Given the Δ of 7, we calculated the sample size to test the null hypothesis H0: $\mu 1 - \mu 0 > 7$ versus the alternative hypothesis H1: $\mu 1 - \mu 0 \leq 7$, where $\mu 1 - \mu 0$ is the mean difference of the time period between the LD group and the RD group (non-inferiority test). Based on 80% power and an $\alpha = 0.05$ significance level, a total of 40 participants were included in each group, for a total of 80 participants, considering a 5% drop-out rate. However, because the study was conducted during the SARS-CoV-2 virus pandemic, which prevented some patients from coming to the hospital, the approximate annual number of hospitalized patients with SAT in our department was 70. Finally, only 78 participants were recruited for this study.

All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) v 26.0 software (SPSS, Inc., Chicago, IL). All tests were performed with the a-level set to 0.05 (2-tailed). Data are presented as mean ± standard deviation, median (inter-quartile range), or numbers (%) as appropriate. The difference between the randomized groups on baseline variables was assessed using the standardized mean difference (SMD). We assessed the effect of the LD group *vs*. the RD group on the primary outcome using a 2-sample t-test. Non-inferiority was claimed when the upper limit of the 2-sided 95% confidence interval (CI) was below the non-inferiority margin. Time period, the mean score for the MMAS-8, neck pain, tenderness at the region of the thyroid gland, and cumulative PDN dose (mg) was presented as a point estimate and corresponding 95% CI [4]. We assessed the treatment effect on normally distributed continuous variables using the 2-sample t-test.

Randomized groups were compared regarding the percentage of relapse during treatment and after treatment using a χ^2 test or Fisher's exact test where appropriate, which were also used to assess differences in the incidence of adverse events between treatments.

Results

The study design is illustrated in Figure 1. Of 77 patients who were recruited from 1 Dec 2020, to 30 Dec 2021, two were excluded, including one who did not meet the inclusion criteria and 2 others who declined to participate in this study. Hence, 74 individuals were enrolled and randomly allocated to the LD group or RD group. All individuals followed the fasting instructions, and none developed adverse side effects. No patient

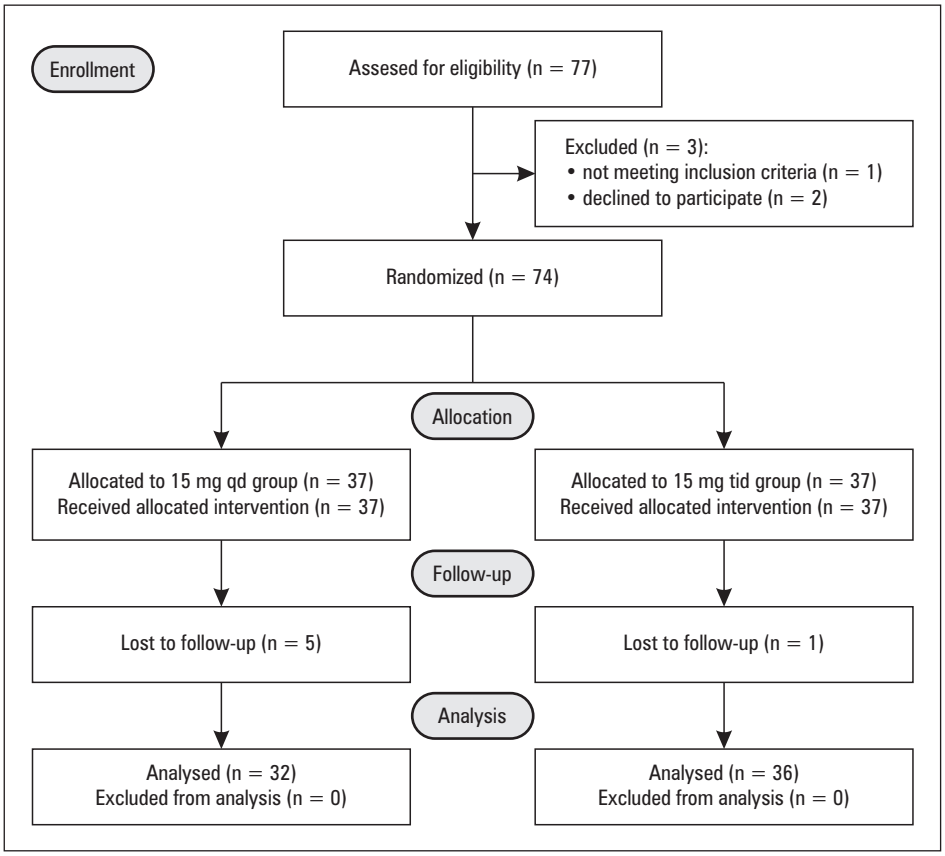

Figure 1. *Trial profile. CONSORT diagram of the study. CONSORT — CON-solidated Standards of Reporting Trials*

quit the study based on the withdrawal criteria. Finally, 68 patients completed the study, and the data of 68 patients were included for statistical analysis.

There were no significant differences in the baseline characteristic of the patients assigned to the LD and RD groups (Tab. 1). The number of patients in the LD and RD groups was 32 and 36, respectively. The LD group consisted of 12 males and 20 females with a median age of 42.16 ± 9.74 (range, 30–71) years, median disease duration before treatment of 11.16 ± 6.49 (range, 3–30) days, and median visual analogue scale (VAS) pain score of 6.44 ± 1.08. The RD group consisted of 14 males and 22 females with a median age of 44.92 ± 11.80 (range, 29–58) years, median disease duration before treatment of 12.69 ± 7.83 (range, 3–32) days, and median visual analogue pain scale (VAS) pain score of 6.11 ± 1.24. There were no significant differences in sex ratio, age, course, and clinical manifestations between the two groups ($p > 0.05$).

In addition, there was no significant difference in treatment duration between the LD and RD groups (55.31 ± 14.05 *vs*. 61.25 ± 19.95 days, respectively, $p = 0.053$). The mean difference in the time period (days) required for PDN treatment between the LD and RD groups was –1.86 [95% confidence interval (CI): –10.64 to 6.92) days, which was within

Table 1. *Baseline characteristics*

	LD group (n = 32)	RD group (n = 36)
Gender		
Male	12 (37.50%)	12 (33.33%)
Female	20 (62.50%)	24 (66.67%)
Age(years)	42.16 (9.74)	44.95 (11.80)
Laboratory findings		
ESR [mm/h]	49.91 (24.95)	65.08 (21.77)
FT3 [pmol/L]	10.37 (4.11)	10.05 (5.27)
FT4 [pmol/L]	32.70 (14.37)	29.56 (14.66)
TSH [mIU/L]	0.53 (1.63)	0.43 (1.43)
Symptoms		
Fever [°C]	6 (18.75%)	8 (22.22%)
Palpitation	0	1 (5%)
Pain score (VAS)	6.44 (1.08)	6.11 (1.24)
Duration of symptoms before treatment (days)	11.16 (6.49)	12.69 (7.83)
Neck pain		
Right/Left, n(%)	5 (15.62%)	11 (30.56%)
Bilateral, n (%)	27 (84.37%)	25 (69.44%)

Data are mean ± standard deviation (SD), median [interquartile rang (IQR)] or number of patients; LD — low-dose; RD — regular-dose; ESR — erythrocyte sedimentation rate; TSH — thyroid-stimulating hormone; FT3 — free triiodothyronine; FT4 — free thyroxine

Table 2. *Primary endpoint and secondary endpoint*

	LD group (n = 32)	RD group (n = 36)	p-value	Treatment difference (LD–RD) (95% CI)
Primary endpoint				
Time period (days)	55.31 ± 14.05	61.25 ± 19.95	0.053[a, b]	–1.86 (–10.64 to 6.92)[c]
Secondary endpoint				
Patients of relapse during treatment	6 (18.75%)	9 (25%)	0.74[d]	/
Patients of relapse after stopping treatment	2 (6.25%)	3 (8.33%)	0.89[d]	/
Drug compliance	5.8 4 ± 0.88	5.33 ± 1.12	0.031[b]	0.51 (0.017 to 1.00)
Time period of symptom vanishing [days]				
Neck pain	2.56 ± 0.90	2.42 ± 0.86	0.63[b]	0.15 (–0.28 to 0.57)
Tenderness at the region of thyroid gland	6.95 ± 1.38	6.24 ± 1.45	0.51[b]	0.72 (0.03 to 1.40)
Cumulative PDN dose [mg]	504.22 ± 236.86	1002.28 ± 309.86	0.046[b]	–498.06 (–632.90 to –363.22)
ESR [mm/h]				
Baseline	49.91 ± 24.95	65.08 ± 21.77	0.39[b]	–15.18 (–26.49 to –3.87)
2 weeks	17.97 ± 12.60	17.23 ± 13.61	0.83[b]	0.74 (–5.63 to 7.12)

Data are presented as mean ± standard deviation (SD), median (inter-quartile range), or number (%); [a]p-value for superiority; [b]data are compared using Student's t test; [c]upper CI limit is less than the noninferiority delta of 7 days, so noninferiority is claimed; [d] data are compared using χ^2 test. LD — low-dose; RD — regular-dose; CI — confidence interval; PDN — prednisone; ESR — erythrocyte sedimentation rate

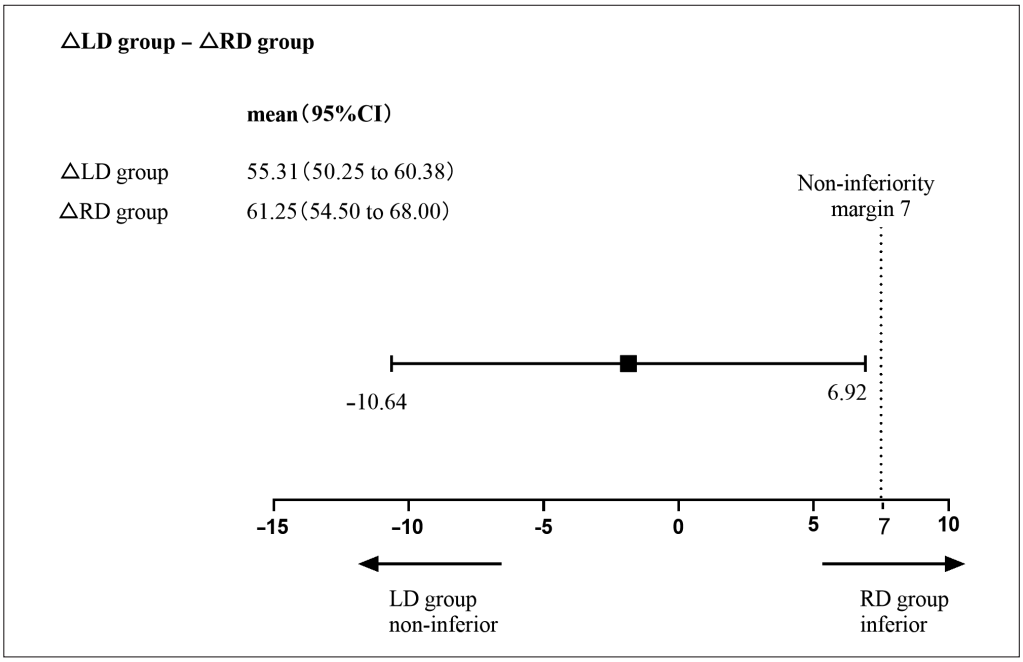

Figure 2. *Primary outcome according to treatment group. Non-inferiority diagram of the mean difference of the period (days) required for prednisone (PDN) treatment between the low-dose (LD) group and the regular-dose (RD) group. The dashed line represents groups. CI — confidence interval*

the non-inferiority margin of 7 days (Tab. 2 and Fig. 2). There was a significant difference in the mean score for the MMAS-8 between the LD and RD groups (5.84 ± 0.88 *vs*. 5.33 ± 1.12, respectively, p = 0.031), but not in the duration of neck pain (2.56 ± 0.90 *vs*. 2.42 ± 0.86 days, respectively, p = 0.63) or tenderness of the thyroid gland (6.95 ± 1.38 *vs*. 6.24 ± 1.45 days, respectively, p = 0.51) (Fig. 3). Also, there was a significant difference in the cumulative PDN dose between the LD and RD groups (504.22 ± 236.86 *vs*. 1002.28 ± 309.86, respectively, p = 0.046) (Fig. 3). There were also significant differences in the erythrocyte sedimentation rate (ESR) at 2 weeks as compared with baseline in both groups. The pre-treatment and post-treatment ESRs

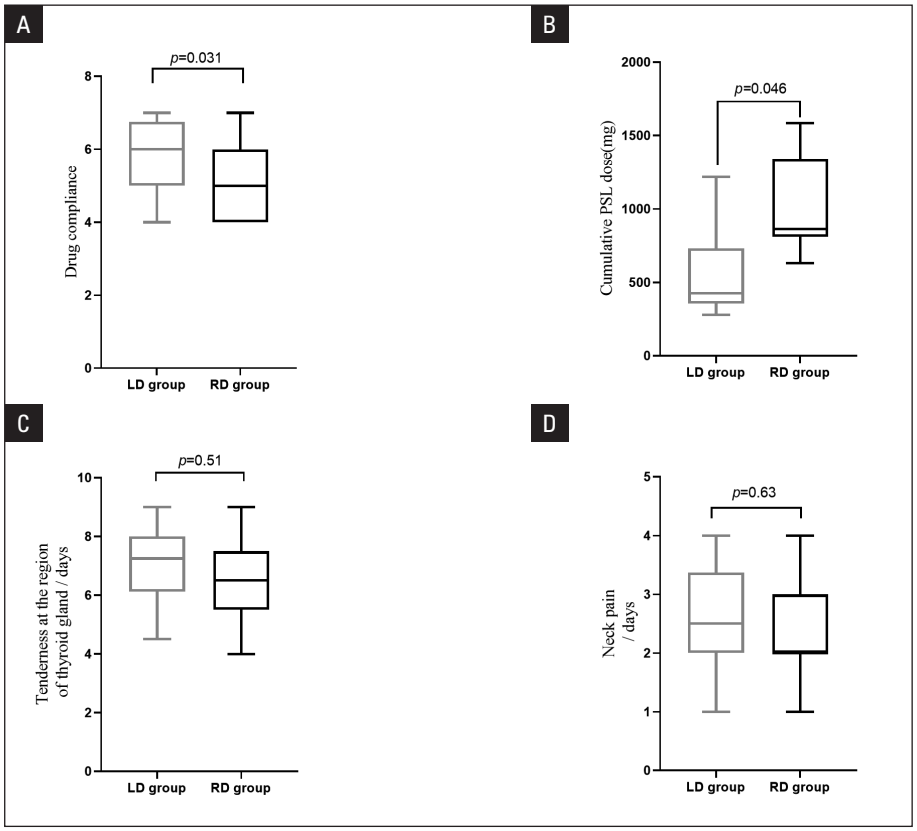

Figure 3. *Comparison of drug compliance, time of disappearance of tenderness at the region of thyroid gland, neck pain, and cumulative prednisone (PDN) dose (mg) between the low-dose (LD) and regular-dose (RD) groups. Boxplots show quartiles and median time taken for normalization;* **A.** *Drug compliance;* **B.** *Time taken for disappearance of tenderness at the region of thyroid gland;* **C.** *Neck pain;* **D.** *Cumulative PDN dose (mg)*

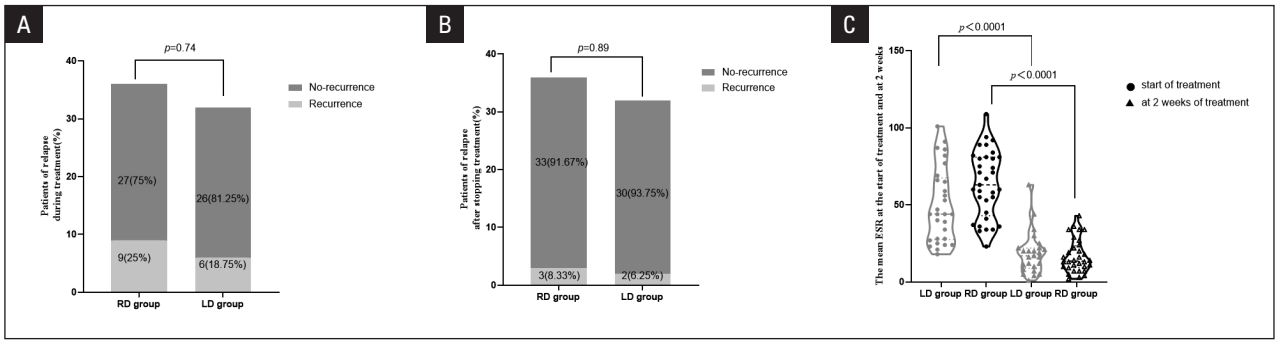

Figure 4. *Comparison of relapse after stopping treatment and during treatment, and the mean erythrocyte sedimentation rate (ESR) at the start treatment and at 2 weeks between the low-dose (LD) group and regular-dose (RD) group. Violin plots show quartiles and median mean ESR of C at the start of treatment and at 2 weeks*

were 49.91 ± 24.95 and 17.97 ± 12.60/mm/h, respectively ($p < 0.0001$) in the LD group, and 65.08 ± 21.77 and 17.23 ± 13.61/mm/h, respectively ($p < 0.0001$) in the RD group, but there was no significant difference between the two groups before and after treatment (Fig. 4). In the LD and RD groups, relapses occurred in 6 (18.75%) and 9 (25%) patients, respectively ($p = 0.74$). After discontinuation of treatment, there was no significant difference in the incidence of relapses between the LD and RD groups [2 (6.25%) *vs.* 3 (8.33%), respectively, $p = 0.89$) (Tab. 2 and Fig. 4).

All adverse events are shown in Table 3. In the LD and RD groups, 5 (15.62%) and 9 (25%) patients experienced adverse events, respectively. The most common adverse event was weight gain followed by gastric discomfort, which occurred at similar rates in

Table 3. *Adverse events in each treatment group*

	LD group (n = 32)	RD group (n = 36)
Adverse events		
All	5 (15.62%)	9 (25%)
Gastrointestinal disorders	1 (3.12%)	1 (2.78%)
Gain weight	2 (6.25%)	1 (2.78%)
Blood glucose increased	0	3 (8.33%)
Hypertension	1 (3.12%)	1 (2.78%)
Insomnia	0	1 (2.78%)
Facial acne	0	1 (2.78%)
Hypothyroidism	1(3.12%)	1 (5.56%)

Data shown as n (%), are based on the safety analysis set (all patients randomly assigned to treatment groups with documented safety data); LD — low-dose; RD — regular-dose

the LD and RD groups. However, the total number of patient-reported adverse events was significantly lower in the LD group than in the RD group. One patient with type 2 diabetes mellitus in the RD group experienced large fluctuations in blood glucose levels during treatment. One patient in the LD group and 2 in the RD group developed temporary hypothyroidism.

Discussion

In this randomized controlled trial, the clinical efficacy and safety of different doses of PDN for the treatment of SAT were compared. The results of this study showed that PDN at the LD and RD was effective for the treatment of moderate to severe SAT with no significant difference in treatment duration, the incidence of recurrent symptoms during treatment, relapse, or time for clinical symptoms to resolve. However, there were significant differences in compliance, total cumulative PDN dose during treatment, and overall adverse events, which are consistent with previous findings that small doses of hormones are associated with fewer adverse effects and good compliance, thereby mitigating potential organ damage. Overall, the use of smaller doses of PDN was not inferior to conventional doses in terms of total treatment duration.

Although the 2016 ATA guidelines recommend the use of NSAIDs for the treatment of mild SAT, the recommended regimen for moderate to severe cases of SAT and patients who do not respond to NSAIDs includes 40 mg of PDN daily for 1–2 weeks and then tapering the dosage for 2–4 weeks depending on the clinical response [4, 8]. However, there is relatively little evidence supporting this regimen. The use of high-dose PDN for the treatment of SAT is often associated with severe side effects that may be intolerable to some patients; thus, several previous studies recommend a starting dose of PDN at 15–60 mg [4, 6, 7, 9–13]. However, in clinical practice, both small and large doses of PDN have been used to treat SAT cases, depending on the preference of the clinician. According to previous reports [6, 9, 10], the mean duration of the conventional dose of PDN for treatment of SAT is about 36 ± 12 days, although patient compliance was poor and the relapse rate was high. Comparatively, the mean total duration of treatment in this study was 55.31 ± 14.05 days in the LD group and 61.25 ± 19.95 days in the RD group. Hence, the treatment duration was shorter with low-dose PDN than with the conventional dose, which may be related to greater patient compliance, which was superior in the LD group than the RD group, as determined by the MMAS-8, and most patients adhered to the treatment regimen and did not change the dosage arbitrarily. Notably, patient compliance directly influences the effect of drug treatment, which is the reason why treatment duration was significantly shorter in the LD group. Nonetheless, the treatment duration in both the LD and RD groups was greater in the present study than the mean values of previous studies, which may be related to the ethnicity of the patients included in previous studies.

The results of the present study suggest that PDN at both the LD and RD are effective for the treatment of SAT. Previous clinical studies have shown that early treatment of SAT with hormones can effectively relieve patient symptoms of thyroid pain and tenderness, improve daily life, and return thyroid function to normal. However, high-dose PDN shock therapy may be an overtreatment because a small dose of PDN is sufficient to achieve recovery while minimizing the risk of hormone-related complications. In contrast, the use of high doses of hormones often causes severe side effects that could be intolerable to some patients [14–21]. Therefore, it is important to control the frequency and dosage of hormone therapy. However, relatively few studies have investigated the efficacy of low-dose PDN for the treatment of SAT to minimize the risk of potential side effects associated with high-dose PDN. Hence, in this study, the efficacy of 2 starting dosages of PDN was compared. The results showed that both regimens were efficacious and achieved the therapeutic goal, although safety and compliance were superior with low-dose PDN, and it significantly reduced the risk of potential organ damage.

According to previous studies, approximately 5–20% of patients experience a relapse of SAT during hormone therapy or after discontinuation [22–24]. The results of the present study showed that 6 (18.75%) and 9 (25%) in the LD and RD groups, respectively, experienced recurrent symptoms at the time of drug

reduction, while only 2 (6.25%) patients in the LD group experienced relapse within 1–2 months after discontinuation, as with 3 (8.33%) patients in the RD group within 3 months after discontinuation. However, there was no significant difference in the recurrence rate during treatment or after discontinuation between the groups, and all patients were treated in the same manner as the initial episode.

Approximately 30% of patients with SAT experience hypothyroidism and most typically regain normal thyroid function within one year [4]. The rate of permanent hypothyroidism in previous studies was 5–15% [5, 21], which was similar to the rates of temporary hypothyroidism of 3.12% and 5.56%, respectively, in the LD and RD groups in the present study. Notably, there was no significant difference in the incidence of temporary hypothyroidism between the LD and RD groups, although it was not possible to compare the rates of permanent hypothyroidism. There are also conflicting data in the literature regarding whether PDN treatment of SAT causes permanent hypothyroidism. Although some previous studies reported higher rates of permanent hypothyroidism with PDN treatment, other studies suggest that hormone therapy may have a protective effect against the development of permanent hypothyroidism [21, 23].

There were several limitations to this study that should be addressed. First, although this study was a prospective randomized controlled trial, the sample size was relatively small, the participants were recruited from a single centre, the follow-up time was relatively short, and the study duration was relatively long, which may have biased the results. Therefore, prospective multicentre studies with large sample sizes and longer follow-up times are needed to verify these results. Second, the primary outcome of this study was the duration of PDN required to resolve symptoms of SAT. The Sars-CoV-2 pandemic prevented some patients from returning to the hospital for follow-up observations at the required time, and thus the days of administration adversely effected some laboratory parameters, including the fact that the ESR and thyroid function of some patients may not have been accurately recorded, which could have biased the study. Due to the relatively short period and the small sample size of this study, some long-term adverse effects, such as permanent hypothyroidism, may have been missed. Therefore, it was difficult to compare the adverse effects between the groups.

Conclusion

The results of this study show that the efficacy of oral PDN was similar between the LD and RD groups, so LD therapy may be sufficient to achieve complete recovery and better outcomes for SAT.

Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

Y.X. wrote the manuscript; Y.C., Q.Z., C.H., B.Z., and J.G. directed the study; X.Z., S.L., and Q.W. supervised the project; J.G. proposed and supervised the project; all authors read and approved the final submitted manuscript.

Conflict of interests

The authors declare no competing interests.

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