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*Review Article*

# Effect of levothyroxine sodium combined with selenium supplement

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**Abstract:** Objective: This study was designed to explore the effect of levothyroxine sodium combined with selenium supplement. Methods: A total of 156 patients with Hashimoto's thyroiditis (HT) were treated in our hospital. Among them, 68 patients that were treated with levothyroxine sodium were regarded as the control group (CG), and 88 patients treated with levothyroxine sodium and selenium supplement were the research group (RG). The efficacy, thyroid function, blood selenium levels, serum total cholesterol (TC) and other related cytokines, thyroid autoantibody (TGAb, TPOAb), goiter and adverse reactions were observed. Results: The total effective rate of the RG was higher than that of the CG ($P<0.05$). After treatment, the thyroid function of the RG was better than that of the CG ($P<0.05$). The blood selenium level in the RG was significantly higher than that in the CG ($P<0.05$). After treatment, the expression levels of TG, TC and LDL-C in the RG were lower than those in the CG ($P<0.05$), and the expression level of HDL-C was higher than that in the CG ($P<0.05$). The TG-Ab and TPO-Ab levels in the RG were lower than those in the CG ($P<0.05$). The goiters in the RG were less than that in the CG ($P<0.05$). The adverse reactions in the RG were lower than those in the CG ($P<0.05$). Conclusion: Levothyroxine sodium combined with selenium supplement is effective in treating HT. It can effectively improve the thyroid function and TC function of patients, with high safety. Hence, it's worth popularizing in clinical use.

**Keywords:** Levothyroxine sodium, selenium supplement therapy, Hashimoto's thyroiditis, thyroid function, TC-related cytokines

## Introduction

Hashimoto's thyroiditis (HT), clinically known as chronic lymphocytic thyroiditis, is a common thyroid disease [1]. It is an autoimmune disease, and is mostly found in female patients [2]. Lymphocytes affect autoantibodies in Hashimoto's thyroiditis patients, which damages the thyroid structure, and increases the indices of thyroglobulin antibody and thyroid peroxidase antibody in the body [3, 4]. HT does not appear with obvious clinical symptoms in the early stage of disease occurrence. Concurrently, many clinical manifestations will appear in the late stages of disease occurrence, which are easily missed or misdiagnosed [5]. Its main symptom is thyroid enlargement without pain, and if it is not treated effectively, it will lead to hypothyroidism or thyroid failure [6]. The life and health of patients are seriously affected. The incidence of HT has been on the rise in recent years [7]. However, its pathogenesis is still not completely clear, and there is no effective treatment for HT [8]. Drug therapy is often used to clinically treat patients to control their thyroid enlargement [9].

According to data, HT patients are mostly treated with high-dose levothyroxine sodium replacement therapy [10], and their condition can be partly improved [11]. Leftthyroxine sodium is suitable for long-term replacement therapy of congenital hypothyroidism and hypothyroidism caused by various reasons in children and adults, and can also be used for inhibition (and replacement) therapy after an operation for a simple goiter, chronic lymphocytic thyroiditis and thyroid cancer [12, 13]. Although levothy-

**Table 1.** Efficacy evaluation

| Efficacy | |
|---|---|
| Cure | Symptoms disappear, thyroid function indices are normal, and there are no adverse reactions. |
| Markedly effective | Symptoms are dramatically improved, thyroid function indices tend to be normal, and there are no adverse reactions. |
| Effective | Symptoms improve, and thyroid function indices improve, accompanied by minor adverse reactions. |
| Ineffective | Symptoms and thyroid function indices do not change or worsen, accompanied by serious adverse reactions. |

roxine sodium can regulate the body-related antibodies of HT patients, it cannot improve their related immune function, and the clinical efficacy is still unsatisfactory [14]. Authors Wu B and Xie C [15] confirmed that levothyroxine sodium had a long treatment period and slow symptom relief, and adverse reactions such as abnormal bone metabolism and hyperthyroidism will occur after long-term continuous use. There are also related studies that selenium supplementation can alleviate the immune dysfunction of HT patients and promote their recovery [16]. Selenium is an essential trace element for human body, and the thyroid gland is one of the organs with the highest selenium content [17]. It has a vital influence on synthesis, metabolism and activation of thyroid hormones [18]. However, we are still unclear about the effect of levothyroxine sodium combined with selenium supplementation on thyroid function of pontine HT patients, and the effect of this scheme on TSH and TC-related cytokines has not been discussed. Therefore, this study will investigate the effects of levothyroxine sodium combined with selenium supplementation on thyroid function, TSH, TC-related cytokines of HT in order to provide direction and a good basis for future clinical treatment.

## Methods

### *Patient data*

A total of 156 HT patients treated in the Third Affiliated Hospital of Anhui Medical University from February 2016 to June 2018 were collected. Among them, 68 cases were treated with levothyroxine sodium replacement therapy and were regarded as a control group (CG) and they were 40.6±6.3 years old on average. While 88 cases were treated by levothyroxine sodium combined with selenium supplementation were considered as the research group (RG) and they were 42.4±5.5 years old on average. This study has been approved by the Medical Ethics Committee of the Third Affiliated Hospital of Anhui Medical University, and all patients were informed and they have signed an informed consent form.

### *Inclusion and exclusion criteria*

Inclusion criteria were as follows: All patients who were treated in the Third Affiliated Hospital of Anhui Medical University for the first time; those diagnosed with HT [19] by the Third Affiliated Hospital of Anhui Medical University; those with complete clinical data and who were willing to be followed up; those informed of the purpose of this research and signed an informed consent form.

Exclusion criteria were as follows: All patients who were allergic to the drugs used; those complicated with other tumors; those with severe inflammation or serious immune deficiency; those with congenital liver, kidney and heart functional defects; and women lactating or pregnant.

### *Treatment methods*

Patients in the CG were treated with levothyroxine sodium alone. The initial dosage was 25 ug, and then it was adjusted once every 2-4 weeks according to the change of disease condition. The upper limit of each adjustment was 25 ug. The maximum dosage did not exceed 159 ug, and it was maintained for continuous treatment. In addition to the treatment with levothyroxine sodium, those in the RG also had selenium supplement therapy, taking selenium yeast tablets orally, twice a day, 50 ug each time. The treatment time of the two groups was 6 months.

### *Outcome measures*

Main outcome measures: The efficacy of patients in the two groups was observed. See **Table 1** [20] for the evaluation standard of efficacy; thyroid function, the levels of free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) in both groups before and after treatment were compared [by automatic biochemical analyzer], and the blood

**Table 2.** General data table

| | Research group (RG) (n=88) | Control group (CG) (n=68) | t or $\chi^2$ | P |
|---|---|---|---|---|
| Age (years) | 42.4±5.5 | 40.6±6.3 | 1.902 | 0.059 |
| BMI (KG/cm$^2$) | 23.52±3.05 | 24.46±4.72 | 1.506 | 0.134 |
| Gender | | | 1.614 | 0.204 |
| Male | 62 (70.45) | 54 (79.41) | | |
| Female | 26 (29.55) | 14 (20.59) | | |
| Living environment | | | 1.010 | 0.315 |
| Cities and towns | 54 (61.36) | 47 (69.12) | | |
| Countryside | 34 (38.64) | 21 (30.88) | | |
| Education level | | | 0.391 | 0.532 |
| < high school | 37 (42.05) | 32 (47.06) | | |
| High school or higher | 51 (57.95) | 36 (52.94) | | |
| History of smoking | | | 2.117 | 0.146 |
| Yes | 24 (27.27) | 26 (38.24) | | |
| No | 64 (72.73) | 42 (61.76) | | |
| History of alcoholism | | | 0.590 | 0.442 |
| Yes | 36 (40.91) | 32 (47.06) | | |
| No | 52 (59.09) | 36 (52.94) | | |
| Family medical history | | | 0.146 | 0.703 |
| Yes | 48 (54.55) | 35 (51.47) | | |
| No | 40 (45.45) | 33 (48.53) | | |
| Nationality | | | 0.093 | 0.760 |
| Han | 79 (89.77) | 60 (88.24) | | |
| Ethnic minorities | 9 (10.23) | 8 (11.76) | | |

**Table 3.** Efficacy assessments of research group and control group [n (%)]

| | Research group (RG) (n=88) | Control group (CG) (n=68) | $X^2$ value | *P* value |
|---|---|---|---|---|
| Cure | 51 (57.95) | 32 (47.06) | 1.829 | 0.176 |
| Markedly effective | 28 (31.82) | 18 (26.47) | 0.528 | 0.468 |
| Effective | 7 (7.95) | 10 (14.71) | 1.801 | 0.180 |
| Ineffective | 2 (2.27) | 8 (11.76) | 5.761 | 0.016 |
| Total effective rate | 86 (97.73) | 60 (88.24) | 5.761 | 0.016 |

selenium levels of both groups before and after treatment were assessed [by atomic fluorescence spectroscopy]; the changes of TG, TC and LDL-C levels of TC-related cytokines before and after treatment between the two groups were compared [by automatic biochemical analyzer], and the changes of TGAb and TPOAb levels of thyroid autoantibody before and after treatment were observed [by automatic biochemical analyzer].

Secondary outcome measures: Before and after treatment, the thyroid diameter in the left lobe, isthmus and right lobe of the two groups were compared [by ultrasonography], and the adverse reactions of both groups were compared.

*Statistical analysis*

The data results were statistically analyzed by SPSS 22.0 statistical software, and the relevant graphs were drawn by Graphpad 7 software. The counting data were expressed by (rate), and inter-group comparison was made with Chi-square test. The measurement data were expressed as (mean ± standard deviation), and inter-group comparison adopted the t test. P<0.05 was seen as a statistically significant difference.

## Results

*Comparison of general data*

There was no difference in age, BMI, gender, living environment, education level, history of smoking, history of alcoholism, family medical history and nationality between the two groups (P>0.05), as shown in **Table 2**.

*Efficacy evaluation*

Through comparing the efficacy of treatment in patients in both groups, we found that the total effective rate of the RG was 97.73% and in the CG it was 88.24%. The total effective rate in the RG was higher than that in the CG, with statistical significance (P<0.05) (**Table 3**).

*Thyroid function of patients in the two groups before and after treatment*

The changes of thyroid function indices of patients in both groups before and after treatment were observed. It turned out that there was no statistical difference in the FT3, FT4 and TSH levels of them before treatment (P>0.05). However, their FT3 and FT4 levels after treatment clearly increased and those in

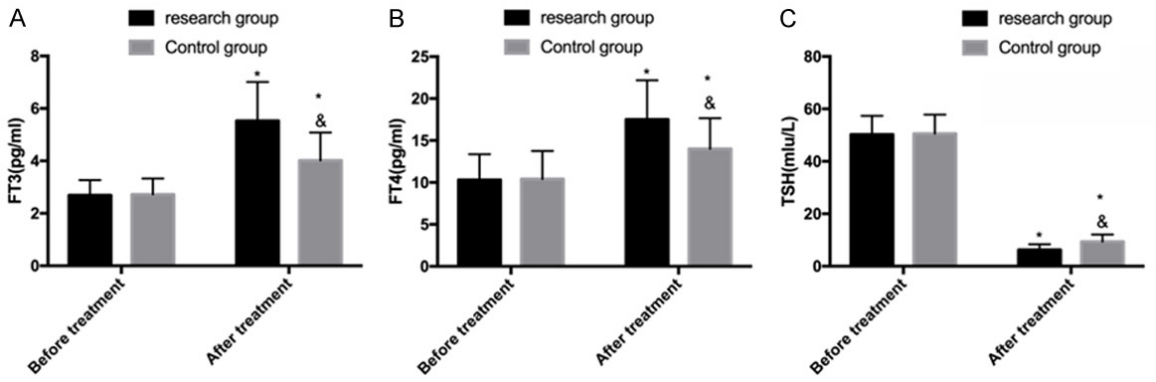


**Figure 1.** Thyroid function of patients in the two groups before and after treatment. A. FT3 expression levels of patients in the two groups before and after treatment. B. FT4 expression levels of patients in the two groups before and after treatment. C. TSH expression levels of patients in the two groups before and after treatment. Note: * indicates comparison with pre-treatment, & indicates comparison with research group.

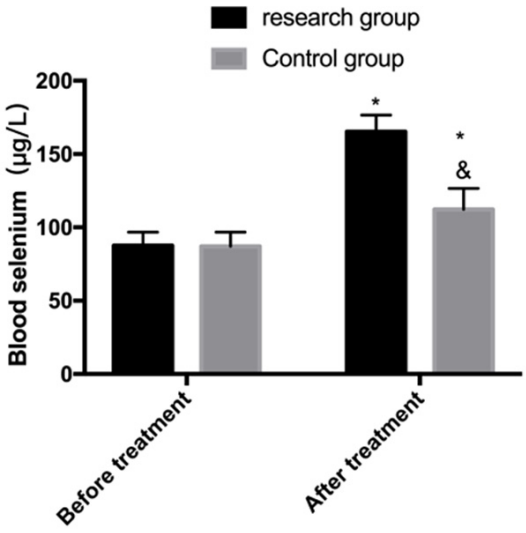


**Figure 2.** Comparison of blood selenium levels of patients between the two groups before and after treatment. * indicates comparison with pre-treatment, & indicates comparison with research group.

the RG were significantly higher than those in the CG (P<0.05). The TSH levels were markedly reduced and those in the RG were significantly lower than those in the CG (P<0.05) (**Figure 1**).

*Comparison of blood selenium levels of patients between the two groups before and after treatment*

The changes of blood selenium levels of patients in both groups before and after treatment were observed. The manifested results were that there was no statistical difference between them before treatment (P>0.05). Their blood selenium levels after treatment clearly increased, and the blood selenium level in the RG was significantly higher than that in the CG, with statistical difference (P<0.05) (**Figure 2**).

*Changes of TC-related cytokines of patients in the two groups before and after treatment*

The blood lipid levels of patients in both groups before and after treatment were compared and analyzed. It was found that their blood lipid levels before treatment were not statistically different (P>0.05). The TG, TC and LDL-C expression levels after treatment were lower than those before treatment, the HDL-C expression levels in the RG were significantly higher than those in the CG (P<0.05), and the HDL-c expression levels in the RG were significantly higher than those in the CG (P<0.05) (**Figure 3**).

*Thyroid autoantibody TG-Ab and TPO-Ab levels in patients in the two groups before and after treatment*

The TG-Ab and TPO-Ab levels of thyroid autoantibodies in patients in both groups before and after treatment were observed. The results displayed that there was no remarkable difference in the TG-Ab and TPO-Ab levels between both groups before treatment (P>0.05). These levels after treatment were lower than those before treatment and those in the RG were significantly lower than those in the CG (P<0.05) (**Figure 4**).

*Comparison of thyroid enlargement of patients between the two groups*

The thyroid enlargement of patients in both groups was compared. Before treatment, there

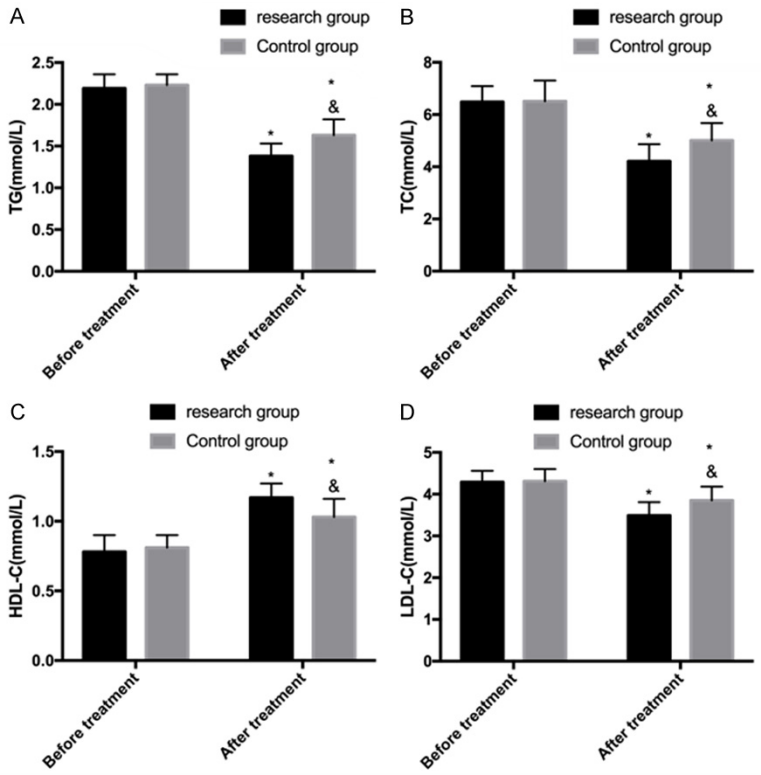


**Figure 3.** Changes of TC-related cytokines of patients in the two groups before and after treatment. A. TG expression levels of patients in the two groups before and after treatment. B. TC expression levels of patients in the two groups before and after treatment. C. HDL-C expression levels of patients in the two groups before and after treatment. D. LDL-C expression levels of patients in the two groups before and after treatment. Note: * indicates comparison with pre-treatment, & indicates comparison with research group.

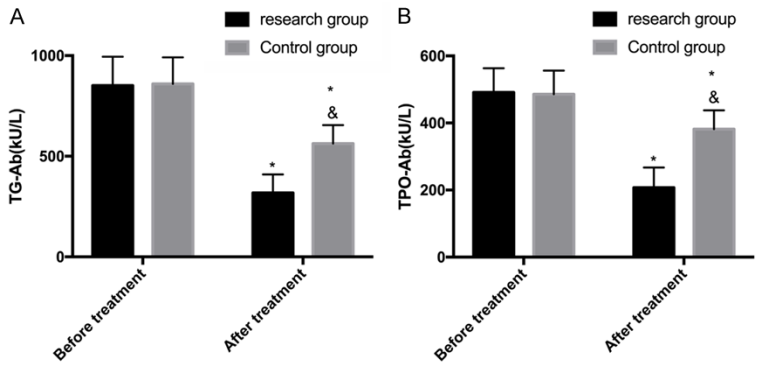


**Figure 4.** Tg-Ab, TPO-Ab index levels of thyroid autoantibody of patients in the two groups before and after treatment. A. Tg-Ab expression levels of patients in the two groups before and after treatment. B. TPO-Ab expression levels of patients in the two groups before and after treatment. Note: * indicates comparison with pre-treatment, & indicates comparison with research group.

was no remarkable difference between both groups in indices of anterior and posterior thyroid diameters (P>0.05). After treatment, the anteroposterior diameters of the left lobe, isthmus and right lobe of both groups were all smaller than those before treatment. The RG was significantly smaller than the CG (P<0.05) (**Figure 5**).

*Adverse reactions of patients in the two groups after treatment*

The incidence of adverse reactions in both groups was observed. The results revealed that the incidence of adverse reactions was 7.95% in the RG and 19.12 in the CG. Their incidence in the RG was significantly lower than that in the CG (P<0.05) (**Table 4**).

## Discussion

HT, also known as chronic autoimmune thyroiditis, is a type of chronic inflammation caused by lymphocytes attacking thyroid follicular cells. Its clinical manifestations are complex and changeable, and its course of disease is slow and long [21]. Accurate diagnosis plays a momentous and indicative part in treating the disease; but the pathogenesis of HT is still not completely clear, and the treatment is limited to symptomatic treatment [22]. Because HT often causes a series of hypothyroid heart diseases, hypothyroidism and blood lipid abnormalities, there is still a lack of accurate medication guidance clinically [23]. However, this study, through exploring the effect of levothyroxine sodium combined with selenium supplement, is quite significant for future clinical treatment of HT patients.

This experiment showed that the clinical efficacy of the RG treated by levothyroxine sodium combined with selenium supplement was sig-

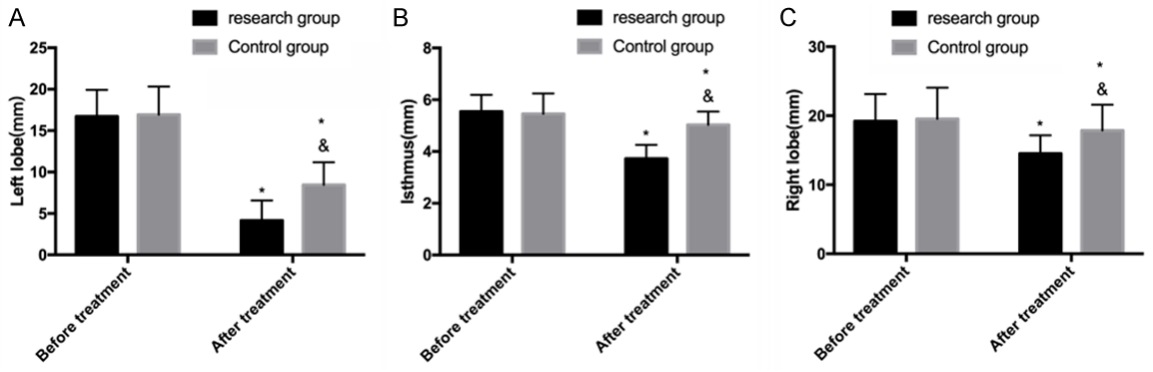


**Figure 5.** Comparison of thyroid enlargement of patients between the two groups. A. Comparison of anteroposterior diameters of left lobe of patients between the two groups. B. Comparison of anterior and posterior diameters of isthmus of patients between the two groups. C. Comparison of anteroposterior diameters of right lobe of patients between the two groups. Note: * indicates comparison with pre-treatment, & indicates comparison with research group.

**Table 4.** Comparison of adverse reactions of patients in the two groups [n (%)]

| | Research group (RG) (n=88) | Control group (CG) (n=68) | $X^2$ | P |
|---|---|---|---|---|
| Nausea | 1 (1.14) | 2 (2.94) | | |
| Fever | 1 (1.14) | 2 (2.94) | | |
| Dizziness and weakness | 1 (1.14) | 2 (2.94) | | |
| Sense of suppression in the chest | 1 (1.14) | 1 (1.47) | | |
| Gastrointestinal discomfort | 2 (2.27) | 3 (4.41) | | |
| Palpitation | 1 (1.14) | 2 (2.94) | | |
| Esophageal irritation | 0 (0.00) | 1 (1.47) | | |
| Incidence of adverse reactions (%) | 7.95 | 19.12 | 4.277 | 0.039 |

nificantly better than that of the CG treated with levothyroxine sodium alone, which also indicated that the efficacy of the former was more remarkable for HT patients. Through consulting previous studies, we found that Barbaro D [24] also proposed that levothyroxine sodium combined with selenium supplement had a more remarkable effect on hyperthyroidism, which also supports our experimental results. Levothyroxine sodium, as a synthetic tetraiodothyronine sodium salt, can be converted into triiodothyronine after absorption by the human body, which can promote the sensitivity of sympathetic-adrenal system and ensure the balance of the physiological organism to some extent. In addition, the ability to regulate lipid metabolism is enhanced by binding specific receptors, which is currently widely used in treating thyroid dysfunction diseases [25]. For example, Romero-Gomez B [26] confirmed that levothyroxine sodium had a better efficacy on patients with hypothyroidism, while Leung AKC and Leung AAC believed that levothyroxine sodium had extremely high safety in treating premature infants with thyroid dysfunction [27]. In this research, by comparing the thyroid function of patients between both groups, we could see that their thyroid function was dramatically improved after treatment compared with that before treatment, which also confirmed the efficacy of levothyroxine sodium on thyroid function. Not only that, levothyroxine sodium could also quickly supplement thyroxine, which was helpful for the recovery of thyroid hormone and the regulation of thyroid pituitary feedback shaft, further improving the recovery of thyroid function. The reason for the marked difference between the two groups was tied to the selenium supplement therapy in our study. At present, it has been proved clinically that selenium is effective in the process of thyroid gland synthesis and metabolism. The lack of selenium can cause abnormal immune metabolism function and decreased thyroxine

secretion, thus causing a series of complications [28]. For instance, the normal operation of blood lipid function is closely regulated by thyroxine [29]. We speculate that the selenium supplement therapy can increase the selenium content in the thyroid gland of patients, it not only helps the oxidation-reduction system of thyroid cells to restore the balance, but also has a strong stimulation effect on the secretion of thyroxine, thus avoiding damage of thyroid cells. In this case, the patients' functional recovery and metabolism can be effectively recovered and maintained. Therefore, through comparing the TC-related indices of patients in both groups after treatment, we discovered that the RG had dramatically better results than the CG. Further, in comparing TG-Ab, TPO-Ab and thyroid enlargement of patients in the two groups, we found that the RG results were superior to the CG, which also confirmed the accuracy of our above conjecture. This revealed that levothyroxine sodium combined with selenium supplement therapy can promote the enhancement of glutathione peroxidase activity and thoroughly eliminate oxygen free radicals in the body, protecting the integrity of cell membranes, further regulating the stability of immune function of patients, improving the efficacy, and reducing the occurrence of chronic inflammatory reactions. Furthermore, we found that there was no statistical difference between patients of both groups by comparing their adverse reactions in the treatment process, which also showed that levothyroxine sodium combined with selenium supplement therapy has high safety and great clinical application prospects.

This research aimed to probe into the efficacy of levothyroxine sodium combined with selenium supplement on HT. Due to limited experimental conditions, there are still deficiencies. For instance, the experimental period is short, the study has not yet conducted prognosis follow-up for patients, and it is not clear how levothyroxine sodium combined with selenium supplement affects their prognosis. Nevertheless, due to the limited number of cases, it may be that some of the results have a chance of statistical bias in calculation. In view of the above deficiencies, we will expand the research sample size and research cycle to obtain more comprehensive experimental results for clinical reference.

## Conclusion

Levothyroxine sodium combined with selenium supplement has clear efficacy on HT, which can effectively improve thyroid function and TC function of patients. It has high safety and is worthy of promotion and use in clinical practice.

## Disclosure of conflict of interest

None.

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