

Original Article

The Clinical Effects of *Ahnjeonbaekho-tang* (AJBHT) on Graves' Disease : A Prospective Clinical Study

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Objectives : Graves' disease is the most common cause of hyperthyroidism, and its pathogenesis includes thyroid specific autoimmunity. Anti-thyroid drugs are widely used for regulating the thyroid function. However, in spite of long-term therapy with anti-thyroid drugs, about 40~70% of the treated patients have a relapse, and some suffer adverse effects. In this study, to evaluate the clinical efficacy of *Ahnjeonbaekho-tang*(AJBHT) on Graves' disease patients, we performed the clinical study prospectively.

Methods : Through the thyroid function test(TFT) of 54 patients diagnosed as Graves' disease in other hospitals, 21 patients were assigned into the study. After the withdrawal of anti-thyroid drugs, AJBHT was administered to patients for 2 months. At the same time, TFT, TSH binding inhibiting immunoglobulin(TBII) level and visual analogue scales (VAS) about fatigue and palpitation were measured before and after administration. Thirteen patients have completed the entire follow-up of this study over two months.

Results : Serum levels of T3 and FT4 were significantly improved by AJBHT(T3: 298.85 ± 79.60 ng/dl 181.15 ± 33.92 ng/dl $p < 0.001$, FT4: 2.78 ± 1.06 ng/dl $\rightarrow 1.78 \pm 0.83$ ng/dl $p < 0.05$). However, there were no significant changes in TSH and TBII values. And the VAS scores of fatigue and palpitation also were significantly improved($5.80 \pm 3.01 \rightarrow 3.60 \pm 2.63$, $p < 0.05$; $6.19 \pm 2.09 \rightarrow 3.60 \pm 2.46$, $p < 0.01$). Patients' age was related to the post-treatment FT4 values($p < 0.05$).

Conclusions : From these results, we suggest that AJBHT is effective on the TFT and the symptoms of Graves' disease, and is a safe alternative drug for Graves' disease patients.

Key Words: Graves' disease, *Ahnjeonbaekho-tang*, thyroid function test, TSH binding inhibiting immunoglobulin, visual analogue scale

Introduction

Graves' disease is the most common cause of hyperthyroidism and the autoimmune disease with thyrotoxicity and diffuse goiter, and presents frequently

ophthalmopathy or sometimes dermopathy¹⁾. Although the etiology is known very little, it is assumed that genetic or environmental causes induce autoantibodies against TSH receptors, leading to the stimulated thyroid²⁾. The prevalence of Graves' disease has no relation to race or the amount of dietary iodide intake, and is found in about 1~2% of population. Considering its prevalence, Graves' disease is a very common disease, and occurs mainly in youth and middle aged persons from twenty to fifty years and is four to ten

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times more frequent in females than in males^{1,3,4}). It's characteristic clinical presentations are heat-intolerance, tachycardia and weight loss²).

Complete treatment for Graves' disease relies on inhibition of anti-thyroid antibodies. However, in western medicine, the present treatment just includes anti-thyroid drug-centered pharmacotherapy, radioiodine therapy, and subtotal thyroidectomy. In Korea, anti-thyroid drugs are preferred for its easy application, to radioiodine therapy and subtotal thyroidectomy because the former usually induces permanent hypothyroidism, and the latter needs a doctor of experienced skill^{1,2}).

However, there are several problems in anti-thyroid drug therapy. First, it is reported that the relapse rate of Graves' disease is even 70% after withdrawal of the drugs. Second, anti-thyroid drugs sometimes cause adverse effects, such as skin rash, myalgia, and granulocytopenia. Third, most Graves' disease patients don't have complete remission of the symptoms in spite of anti-thyroid drug therapy. Fourth, occasionally thyroid hormone levels are not normalized in spite of that therapy^{1,2,5}). Therefore, Graves' disease patients who want Oriental medical therapy increase in number.

From an Oriental medical point of view, it is known that Graves' disease belongs to the category of Young(瘰), Younglew(瘰癧), Goranengjeong(鵲眼凝睛), Toan(兔眼), Sogal(消渴), Jeongchoong(怔忡), Gyounggye(驚悸) or Bunjo(煩躁), which usually fall under Bonhupyosil(本虛標實), and that its major pathological changes include Emhuhwawang(陰虛火旺) or Emhuhwadong(陰虛火動)⁶). However, at present there are no newly reported clinical studies for Graves' disease except one case report⁷) and a study about anti-thyroid drug resistance Graves' disease⁶), which are clinical studies for hyperthyroidism or Graves' disease.

Hence, we expanded the study about anti-thyroid drug resistance to Graves' disease, and analyzed the

effects of *Ahnjeonbaekho-tang*(AJBHT) on the symptoms of general Graves' disease patients and the anti-thyroid antibody excluded in the previous study. Consequently, we have founded significant results to publicize.

Subjects and methods

1. Subjects

We performed thyroid function tests (TFT), anti-thyroid antibody tests and the analysis of clinical symptoms for fifty-four patients who visited the 6th internal medicine outpatient clinic of the Oriental Medicine Hospital of Kyung-Hee Medical Center from 2004 March to 2005 April. Then, 31 patients showed abnormal TFT values, and 21 patients among them consented to this study. And we performed a prospective study, and finally followed up a total of 13 patients over two months. These patients have no disease other than Graves' disease and took no other medicine than AJBHT during the study period.

2. Methods

Every patient consented to withdrawal of anti-thyroid drugs and was administered an AJBHT extract(*Puerariae Radix* 20g, *Scutellariae Radix* 8g, $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ 4g, *Platycadi Radix* 4g, *Angelicae tenuissimae Radix* 4g, *Cimicifugae Rhizoma* 4g, *Glycyrrhizae Radix* 4g) in codex of the Oriental medicine hospital three times a day over two months. Before administration, we performed a thyroid function test and anti-thyroid antibody test, and evaluated the most common chief complaints of patients, fatigue and palpitation, by a Visual Analogue Scale(VAS), which was repeated every month after administration. We made patients point a spot between no symptom(0) and very severe symptom(10) on a 10 cm length stick to evaluate VAS, and made patients recognize a prior

Table 1. The Clinical Characteristics of Study Populations

Case	Age	Sex	Disease duration (month)	Pre- anti-thyroid	Adverse effects	Clinical Symptoms				
						Fatigue	Palpitation	Heat intolerance	Excess sweating	Weight loss
1	37	M	18	○	○	○		○		
2	50	F	36			○	○	○		○
3	5	F	12			○	○			
4	21	F	12	○	○	○	○			
5	28	F	1	○		○	○	○	○	
6	30	F	42	○		○	○	○		
7	35	F	96	○			○			
8	28	F	10	○		○	○	○	○	○
9	46	F	1				○		○	○
10	32	M	36	○		○	○			
11	39	M	2		○	○		○		○
12	31	F	24	○		○	○		○	
13	32	F	5	○	○		○			

pointed spot before every evaluation of VAS. Thyroid function test included TSH (Thyroid stimulating hormone), T3 (Triiodothyronine), T4 (Thyroxine) and Free T4 (FT4), and anti-thyroid antibody test was TSH binding inhibiting immunoglobulin(TBII) test. Each test was requested to be done by the clinical laboratory at Kyung-Hee Medical Center.

3. Statistics

The statistical significance of differences between pre-treatment and post-treatment values in TFT and VAS were tested by a paired sample *t*-test with GraphPad PRISM statistical package(ver. 2.00, GraphPad software inc., San Diego, USA), and the correlations between the therapeutic effects of AJBHT and clinical characteristics were analyzed by multivariate analysis. Each value of TFT and VAS was represented by a mean \pm S.D. For a two-tailed test, a *p* value less than 0.05 was regarded to be statistically significant.

Results

1. Clinical characteristics of study subjects

Subjects participating in this study were comprised of 10 females and 3 males. Their mean age and mean disease duration were each 31.9 ± 11.1 (5~50) years and 22.69 ± 26.14 months. Nine of them had been administered anti-thyroid drugs before our hospital visits and 4 subjects had not, three of whom had withdrawn anti-thyroid drugs without their doctor's permission and one by doctor's advice because of severe adverse effects (granulocytopenia).

Of these subjects, those who suffered the adverse effects of anti-thyroid drugs were four, two with liver function abnormality, one with granulocytopenia and one with skin rash. The most common complaints of the subjects were severe fatigue and palpitation, with 10 and 11 cases of each. The next commonest were heat intolerance, excess sweating, weight loss, each with 5, 4 and 4 cases, and the others were 3 cases of ophthalmopathy and 2 cases of irregular menstruation (Table 1).

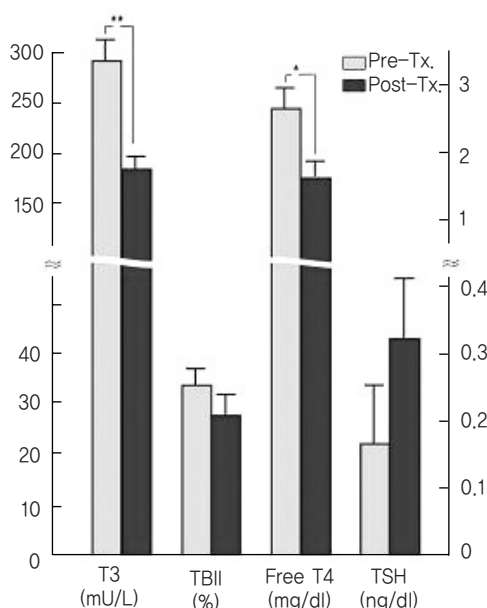


Fig. 1. The effects of Ahnjeonbaekho-tang(AJBHT) on thyroid funtion & thyroid auto-antibody testa. a T3, Triiodothyronine; FT4, Free T4; TSH, Thyroid stimulating hormone; TBII, TSH Binding Inhibiting Immunoglobulin.

* $p < 0.05$, ** $p < 0.01$

2. The effects of AJBHT on thyroid hormone regulation

At the baseline, T3 values were significantly improved from pre-treatment 298.85 ± 79.60 ng/dl to post-treatment 181.15 ± 33.92 ng/dl ($p < 0.001$). Pre-treatment T3 values of all subjects were over the normal values, then after treatment, T3 values of all except three subjects significantly improved to a normal range. FT4 values also significantly improved from pre-treatment 2.78 ± 1.06 ng/dl to post-treatment 1.78 ± 0.83 ng/dl ($p < 0.05$). TSH values were improved from pre-treatment 0.18 ± 0.25 μ U/ml to post-treatment 0.32 ± 0.41 μ U/ml; however, these were not statistically significant. Also, TBII values improved pre-treatment 32.82 ± 13.32 % to post-treatment 27.69 ± 17.19 %; however, these were not statistically significant (Table 2, Figure 1).

3. The effects of AJBHT on clinical symptoms

To evaluate the effects of AJBHT on clinical symptoms, we analyzed the differences between pre-treatment scores and post-treatment scores in the most common complaints, fatigue and palpitation, by using VAS. In VAS of fatigue, the score significantly improved from pre-treatment 5.80 ± 3.01 to 3.60 ± 2.63 ($p < 0.05$), and likewise in VAS of palpitation, from 6.19 to 3.60 ± 2.46 ($p < 0.01$) (Table 3, Figure 2).

4. The correlations between the effects of AJBHT and clinical characteristics

To survey the correlations between the effects of AJBHT on T3, FT4, TSH, VAS and clinical characteristics, we performed multivariate analysis of age, sex, disease duration, thyroid hormone levels and TBII. As a result, the older the subject, the lesser post-treatment FT4 values ($p < 0.05$).

Table 2. The Change of TFT & TBII according to the Treatment^a

Case	T3		TSH		FT4		TBII	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	203	193	0.94	1.27	1.48	1.47	41	25.7
2	207	145	0.02	1.19	1.01	1.04	29.4	52.3
3	331	171	0.15	0.14	2.96	3.12	59.6	54.1
4	423	237	0.09	0.19	2.72	1.56	35.3	5.4
5	284	206	0.07	0.11	3.11	1.89	28	11.3
6	262	166	0.1	0.16	3.57	1.76	28	19
7	308	151	0.1	0.08	3.15	1.65	34.9	24.1
8	283	237	0.08	0.18	2.35	3.6	39.2	57.8
9	161	0.08	0.18	3.27	1.32	30.6	26.5	
10	244	222	0.44	0.12	2.34	2.57	0.1	14.3
11	357	166	0.1	5.19	1.29	31.9	27.4	
12	217	0.08	0.22	1.73	0.85	25.6	10.8	
13	303	147	0.03	0.16	3.32	1.08	43.1	31.3

a TFT, Thyroid Function Test; T3, Triiodothyronine (Normal range : 80~200 ng/dl); FT4, Free T4 (Normal range : 0.8~1.8 ng/dl); TSH, Thyroid stimulating hormone (Normal range : 0.3~4.0 μ U/ml); TBII, TSH Binding Inhibiting Immunoglobulin; Pre, Pre-treatment; Post, Post-treatment.

Table 3. The Changes of VAS Score according to the Treatment

Case	Fatigue		Palpitation	
	Pre	Post	Pre	Post
1	4	4	None	None
2	8	4	6	3
3	2	1	8	7
4	2	1	4	2
5	8	7	6	6
6	9	6	3	3
7	None	None	8	2
8	9	1	9	1
9	None	None	7	2
10	2	2	None	None
11	6	2	6	2
12	8	8	8	8
13	None	None	3	3

Discussion

Although Graves' disease is one of the most common

endocrine diseases, its etiology is not clear, and it is assumed to be a kind of autoimmune disease. Graves' disease patients have antibodies against TSHR (thyroid stimulating hormone receptor), and these anti-TSHR antibodies lead to excess secretion of thyroid hormone. In addition to these stimulatory TSHR antibodies, there are also other anti-thyroid antibodies such as anti-TPO (anti-thyroid peroxidase) antibodies in Graves' disease patients. However, they are considered to be a secondary phenomenon of thyroid tissue destruction⁸⁾.

Clinical presentations of Graves' disease may include all symptoms and signs of thyrotoxicosis. It is known that nervousness, excess sweating, heat intolerance, palpitation, fatigue, weight loss appear 99%, 91%, 89%, 89%, 88% and 85% of the patients as the symptoms of Graves' disease, and that other symptoms, such as ophthalmopathy and thyroid enlarging also appear frequently⁹⁾.

The diagnosis of Graves' disease is not difficult, if the

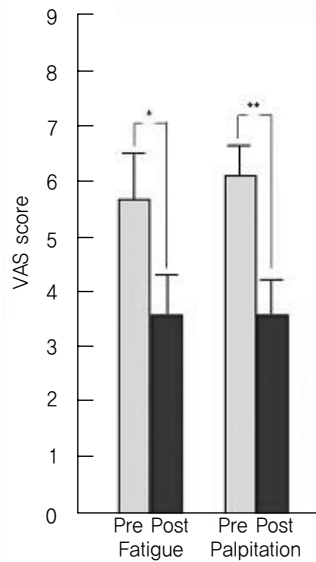


Fig. 2. The Effects of *Ahnjeonbaekho-tang*(AJBHT) on VAS scores of clinical symptomsa. a VAS, Visual analogue scale; Pre, Pre-treatment; Post, Post-treatment.

* $p < 0.05$, ** $p < 0.01$

patient clinically has the symptoms of thyrotoxicosis and diffuse goiter, and definite when increase of thyroid hormone, decrease of TSH and existence of anti-thyroid antibodies are confirmed in serum.

In western medicine, Graves' disease patients are treated by anti-thyroid drugs, radioiodine therapy and subtotal thyroidectomy²⁾. In Korea, however, most of the patients are treated only by anti-thyroid drugs. These anti-thyroid drugs include antiroid(PTU) and met-himazole(MMI), which mainly inhibit TPO from coupling iodotyrosines as well as oxidation and organification of iodides entered the thyroid. In addition, PTU inhibits the conversion of T4 to T3 in peripheral tissues^{1,10,11)}. However, any anti-thyroid drugs cannot remove the main etiology of Graves' disease, anti-thyroid antibodies nor inhibit the production of them.

AJBHT is made out of adjusted *Galgenhaegi-tang*(葛根解肌湯) according to the pathophysiology of

Graves' disease. Graves' disease is *Gonyul*(困熱) resulted from *Mokgibulgep*(木氣不及), and corresponds to *Yangmyunggyung-byung*(陽明經病) of *Sanghanlon*(傷寒論), which presents fever, sweating, non-chilling, paradoxical heat-intolerance. Therefore, we expected that Graves' disease patients would improve by adjusted *Galgenhaegi-tang*(葛根解肌湯) suitable for treating *Yangmyunggyung-byung*(陽明經病).

The fact that the subjects are mostly female in this study corresponds to the report that Graves' disease is six to eight times more common in females than in males. And the fact that mean age is 31.9 ± 11.1 years also corresponds to the frequent onset age of Graves' disease⁹⁾. Although 8 of 13 subjects were administered anti-thyroid drugs before the study, most of them had abnormal values of T3, FT4 and TSH. This may be considered the results of their insufficient drug dosage, so the increase of dosage may be recommended.

However, it is needed to consider other therapeutic methods because 4 of the subjects suffered the adverse effects of anti-thyroid drugs. In addition, it is assumed that it works by other mechanism than the inhibition of TPO because those who poorly respond to anti-thyroid drugs were improved with AJBHT.

In the results, administration of AJBHT for 2 months significantly improved thyroid hormone levels. TFT values of all subjects were improved except FT4 and TSH of each 3 subjects. However, in TSH and anti-thyroid antibody, the degree of improvement is not statistically significant, which is because hypothalamus-thyroid axis may remain inhibited even after thyrotoxicosis state completely resolved^{12,13}. Therefore, measuring FT4 is the best way that we could evaluate those patients' physiological conditions. And considering the fact that anti-thyroid antibody can remain or relapse in spite of anti-thyroid drugs therapy even for one to two years, the period of this study was too short to detect the decrease of anti-thyroid antibodies. Therefore, we may detect the better effects of AJBHT with longer administration.

The most common symptoms of subjects were fatigue and palpitation the same as Byun's report⁵. AJBHT effectively improved the symptoms of subjects who complained about them in spite of anti-thyroid drug therapy. Moreover, there were no adverse effects with AJBHT unlike anti-thyroid drugs.

In analyzing the correlation between thyroid hormone improvement by AJBHT treatment and clinical characteristics, such as age, sex and disease duration, the older the subjects were, the better FT4 became. Therefore, it is assumed that older patients may obtain the better effects of AJBHT and more satisfaction from the treatment.

In this study, the reason why we couldn't discover the correlations between the effects of AJBHT and TBII are these; First, it is difficult to identify the correlations of

Graves' disease and the degree of TBII because its normal range is too wide. So, it is possible only to decide positive or negative aspects of it. Second, it takes TBII at least two years to disappear in administration of anti-thyroid therapy^{1,14}.

Conclusion

We performed this study to evaluate the clinical effects of AJBHT and found out that AJBHT treatment improved thyroid hormone levels and clinical symptoms effectively and that the older the subjects were, the more FT4 improved. In addition, there were no adverse effects in relation to AJBHT. Therefore, it is thought that AJBHT may be used as a safe alternative drug for Graves' disease patients, particularly for the older patients. And it is needed to study for a longer period as well as additional study about the mechanism of AJBHT.

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