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Original Article

Effects of high-dose hormone therapy in patients with thyroid-associated orbitopathy and its effect on visual acuity and ocular surface

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Abstract: Objective: To explore the effects of high-dose hormone therapy (HHT) in patients with thyroid-associated orbitopathy and its effect on visual acuity and ocular surface. Methods: A total of 68 patients with thyroid-associated orbitopathy were randomized into a control group (n=34 cases and 47 affected eyes) treated with prednisone acetate tablets and an observation group (n=34 cases and 51 affected eyes) treated with HHT. After 6 months of medical intervention, the clinical treatment efficacy, visual acuity, ocular surface changes, life of quality and drug safety were compared between the two groups. Results: The degree of eyeball protrusion and palpebral fissure length (PFL) in the observation group were higher than those of the control group 6 months after treatment (P<0.05). The Clinical Activity Score Scale (CAS) scores of the two groups were lower at 1, 3 and 6 months after treatment than before treatment (P<0.05). The CAS score of the observation group at 1, 3 and 6 months after treatment was lower in observation group than control group (P<0.05). The visual acuity of the observation group at 1, 3 and 6 months was better than that of the control group (P<0.05). The observation group showed higher levels of TMH, BUT, and SIt after 6 months of treatment than the control group (P<0.05). The quality of life of the observation group was higher than that of the control group at 6 months after treatment (P<0.05). No significant difference was found in the incidence of adverse reactions between the two groups during the treatment (P>0.05). Conclusion: HHT in patients with thyroid-associated orbitopathy exhibited higher short-term treatment efficacy and improved visual acuity, ocular surface environment as well as quality of life, without increasing the incidence of adverse reactions.

Keywords: High-dose hormone therapy, thyroid-associated orbitopathy, short-term efficacy, visual acuity level, ocular surface environment

Introduction

Thyroid-associated orbitopathy (TAO) is an autoimmune disease [1]. Clinical studies [2] have shown that most patients with orbitopathy may develop clinical or laboratory indications of abnormal thyroid function. Orbital diseases may occur even in patients with a normally functioning thyroid, the leading cause of monocular/binocular protrusion. Studies [3] have shown that most patients with TAO are accompanied by hyperthyroidism that occurred within 18 months prior the onset of thyroid dysfunction, and there is a relationship between orbital lesions and the nature and treatment of hyperthyroidism. Epidemiological survey shows that there are differences in genetic susceptibility of hyperthyroidism, and the number of female patients is 4-5 times that of male patients, which is related to histocompatibility gene locus HLA-DR. Hyperthyroidism has been clinically proven to be associated with thyroid-associated eye disease, pretibial myxedema, immune thyroid disease, cell regulation/humoral regulation mechanisms [4, 5]. Since the early symptoms of TAO patients are mild, some patients may only present with eyeball protrusion, which makes clinical diagnosis and treatment more difficult [6]. Therefore, it is of great significance to strengthen the early treatment and intervention of patients with TAO.

The occurrence and development of TAO is complex. Failure to take effective intervention measures after diagnosis will increase the risk of ocular surface diseases and affect the prog-

Table 1. Baseline data

Item		Observation group (n=34)	Control group (n=34)	χ^2/F	P
Gender (n)	Male	20 (58.82)	18 (52.94)	1.693	0.793
	Female	14 (41.18)	16 (47.06)		
Age (year)		40.15±4.31	40.17±4.33	1.112	0.415
BMI (kg/m^2)		24.04±2.16	24.11±2.19	0.794	0.559
Course		16.32±2.16	16.33±2.17	1.638	0.491
With hypertension		6 (17.65)	5 (14.71)	1.396	0.641
With Hyperlipidemia		9 (26.47)	8 (23.53)	0.857	0.437
With diabetes		8 (23.53)	7 (20.59)	1.121	0.791
History of myocardial infarction		6 (17.65)	7 (20.59)	0.897	0.743
Affected eyes	Left	21 (61.76)	20 (58.82)	1.437	0.558
	Right	13 (38.24)	14 (41.18)		

nosis. Glucocorticoids, orbital radiotherapy, plasma exchange, somatostatin analogs, and orbital decompression are commonly used treatment options for TAO patients [7]. Clinical studies [8] have shown that there is no special treatment for TAO patients with mild symptoms, and it is a good choice to improve thyroid function and lifestyle. For patients with severe symptoms, HHT is needed. HHT can effectively inhibit connective tissue hyperplasia and reduce capillary permeability. At the same time, the use of HTT can reduce the exudation of inflammatory factors, reduce immunosuppression and inflammatory cell infiltration, and help improve the patient's visual acuity and ocular surface changes [9, 10]. Therefore, this study targeted patients with TAO to explore the efficacy of HHT.

Materials and methods

Baseline data

A total of 68 patients with TAO from April 2018 to March 2020 were enrolled and were divided into a control group (n=34 cases, 47 affected eyes) and an observation group (n=34 cases, 51 eyes) using a random number table. This study was approved by the hospital ethics committee, and all treatments were completed with the consent of the patients. The baseline data of the two groups was not statistically different (P>0.05, **Table 1**).

Inclusion criteria: (1) Patients who met the TAO diagnostic criteria [11], and were confirmed by ultrasound, CT scan, and MRI examination; (2) Patients with a European Graves Clinical Activity Score (CAS) (amended by EUGOGO) of ≥ 3 points and with disease in an active stage [12, 13]; (3) Patients with indications to prednisone acetate tablets, HHT, and could tolerate the treatment.

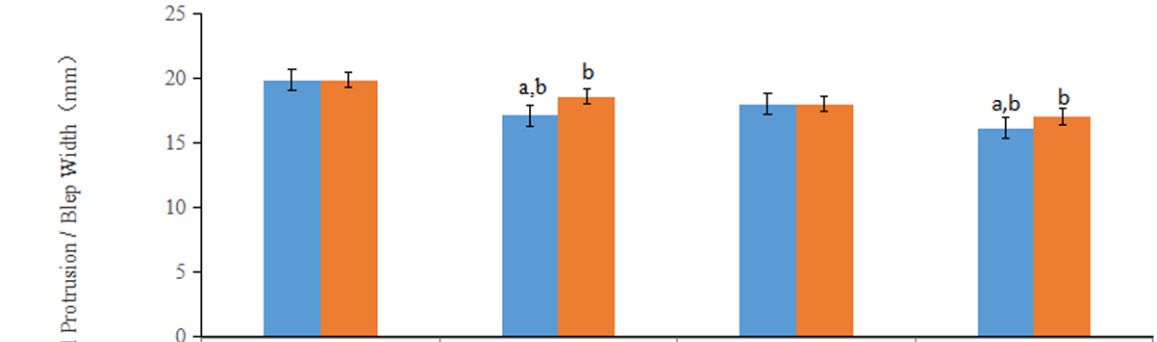
Exclusion criteria: (1) Patients with mental disorders, blood system diseases or autoimmune diseases, *e.g.* Sjogren's syndrome, rheumatoid arthritis; (2) Patients with a history of eye allergies ocular trauma, limbal stem cell deficiency or ocular surface diseases; (3) Patients with abnormal cognitive function and/or those who were prescribed anesthetics and sedatives.

Methods

Preparation before treatment: After admission, both groups received relevant examinations and were given relevant information about TAO, including the type of disease, clinical manifestations, *etc.*, so as to improve the patient's cooperation and compliance.

General treatment: Tobramycin eye ointment was given and routine eye care was performed. At the same time, gastric mucosa protection and potassium and calcium supplement interventions were given during the treatment [14].

Treatment regimens: The control group was treated with prednisone acetate tablets. The initial dose (Sansai Shiqi Pharmaceutical Co., Ltd., H44023869, 5 mg) was 15-40 mg/d, taken orally, and the drug dose was appropriately increased according to the patient's condition. The maximum daily dose was 60 mg; after recovery, the dose was gradually reduced, and maintained at 5-10 mg for 6 months. The observation group was treated with HHT for 6



	Eyeball Protrusion		Eyelid Width	
	Before Therapy	6 Months After Treatment	Before Therapy	6 Months After Treatment
Observation Group	19.85	17.11	17.98	16.14
Control group	19.86	18.59	17.99	17.03

Figure 1. Comparison of short-term efficacy between the two groups. The eyeball protrusion and PFL in the observation group and the control group at 6 months after treatment were lower than those before treatment ($P<0.05$). The measures in the observation group were higher than the control group ($P<0.05$). Compared with the control group, [a]$P<0.05$; compared with before treatment, [b]$P<0.05$.

months. The initial dose of methylprednisolone injection (Zhejiang Xianju Pharmaceutical Co., Ltd., H20023134, 2 ml:50 mg) was I.V. 15 mg/kg each time; the dose was gradually reduced to 7.5 mg/kg for 10 days. After that, intravenous therapy was ceased and 40-60 mg prednisone acetate tablets were prescribed daily. The monthly dose was reduced by 5-10 mg/d, and finally maintained at 5 mg/d.

Outcome measurement: (1) Clinical efficacy: The degree protruding of the eyeball and the length of the palpebral fissure were measured before and after 6 months of treatment in both groups [15]. (2) Clinical Activity Score Scale (CAS score): The CAS scale was used to evaluate the clinical symptoms before treatment and at 1, 3, and 6 months after treatment. The total score was 10 points. A lower score indicates better treatment effect [16]. (3) Vision acuity: The standard visual acuity chart was used to measure the visual acuity of the two groups before treatment and at 1, 3 and 6 months after treatment [17]. (4) Changes in ocular surface: Before treatment and 6 months after treatment, the central tear height (TMH), break-up time of the tear film (BUT), corneal fluorescein (FL) staining, redness scan (R-scan), and Schirmer I test (SIt) were measured [18]. (5) Quality of life: Before and after 6 months of treatment, the two groups were evaluated from physiological field (5 items), psychological field (3 items), independence field (5 items), environmental field (4 items) and social relationship field (4 items). A higher score indicates higher quality of life [19]. (6) Drug safety: The incidence of infection, gastrointestinal discomfort, abnormal blood pressure, abnormal liver and kidney functions, and dizziness were recorded during the treatment.

Statistical analysis

Data were processed by SPSS 18.0 software. The count data were tested by χ^2 test, and represented by n (%), and the measurement data were tested by t test, and were represented by ($x \pm s$). The data of multiple time points were analyzed by analysis of variance. $P<0.05$ was statistically significant.

Results

Comparison of eyeball protrusion and PFL between the two groups

The eyeball protrusion and PFL in the observation group and the control group at 6 months after treatment were (17.11±0.86, 18.59±0.93) mm and (16.14±0.81, 17.03±0.98) mm, respectively; which were lower than (19.85±1.49, 19.86±1.51 mm) and (17.98±1.64, 17.99±1.66) respectively, before treatment ($P<0.05$). Those in the observation group were higher than those in the control group (**Figure 1**, $P<0.05$).

Table 2. CAS comparison ($\bar{x} \pm s$)

Group	Cases	Before treatment	After 1 month	After 3 months	After 6 months
Observation group	34	8.91±1.31	7.45±0.95	5.63±0.71	3.16±0.65
Control group	34	8.90±1.29	8.23±1.18	7.41±0.92	5.34±0.77
Intergroup		F=5.758		P=0.033	
Time point		F=6.332		P=0.018	
Intergroup · time point		F=5.093		P=0.032	

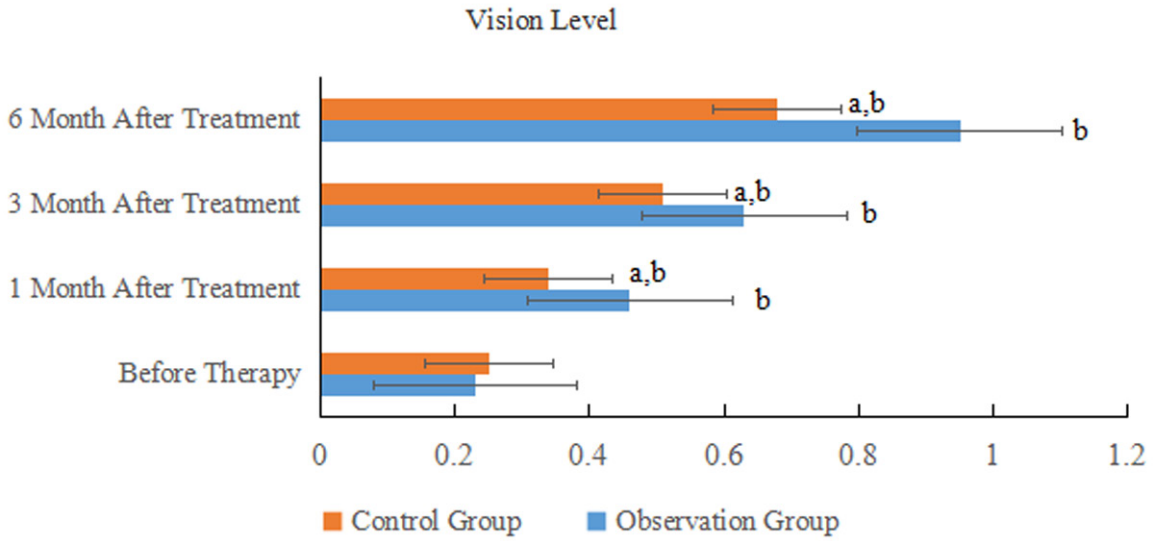


Figure 2. Comparison of visual acuity between the two groups. No significant difference was observed in the visual acuity of the two groups before treatment. The visual acuity of the two groups before treatment was significantly lower than that at 1, 3 and 6 months after treatment (P<0.05). The visual acuity levels at 3 and 6 months in observation group were higher than those in the control group (P<0.05). Compared with the control group, [a]*P*<0.05; compared with before treatment, [b]*P*<0.05.

Comparison of the CAS scores between the two groups

No statistical significance was found in the CAS score of the two groups before treatment (*P*>0.05). The CAS score of the observation group was lower than that of the control group at 1, 3, and 6 months after treatment (*P*<0.05, **Table 2**).

Comparison of visual acuity between the two groups

No significant difference was observed in the visual acuity of the two groups before treatment. The visual acuity of the two groups before treatment was significantly lower than that at 1, 3 and 6 months after treatment (*P*<0.05). The visual acuity levels at 3 and 6 months in observation group were higher than those in the control group (**Figure 2**, *P*<0.05).

Comparison of changes in ocular surface between the two groups

The levels of TMH, BUT, and SIt in the two groups were higher than those before treatment (*P*<0.05) while levels of R-scan and FS were lower than those before treatment (P< 0.05). The R-scan and FS of the observation group were lower than those of the control group (**Table 3**, *P*<0.05).

Comparison of quality of life between the two groups

There was no significant difference in quality of life between the two groups before treatment (P>0.05). After 6 months of treatment, the quality of life in the observation group was higher than that in the control group (**Figure 3**, *P*<0.05).

Table 3. Comparison of changes in ocular surface between the two groups ($\bar{x} \pm s$)

Group		TMH (mm)	BUT (s)	R-scan	FS	SIt (mm)
Observation group (n=34)	Prior to treatment	0.21±0.08	4.58±0.41	2.45±0.41	7.39±0.42	9.86±0.61
	6 months post treatment	0.25±0.11[a,b]	5.21±0.46[a,b]	2.05±0.32[a,b]	7.11±0.37[a,b]	10.42±0.68[a,b]
Control group (n=34)	Prior to treatment	0.20±0.07	4.59±0.43	2.46±0.42	7.41±0.43	9.87±0.63
	6 months post treatment	0.23±0.09[b]	4.82±0.44[b]	2.31±0.36[b]	7.24±0.41[b]	9.97±0.63[b]

Compared with the control group, [a]P<0.05; compared with before treatment, [b]P<0.05.

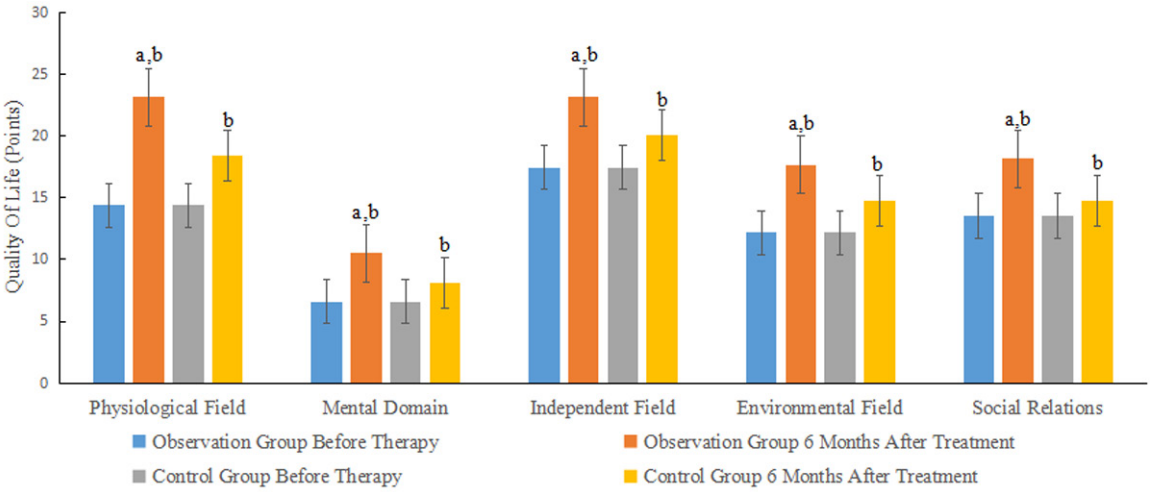


Figure 3. Comparison of quality of life between the two groups. There was no significant difference in quality of life between the two groups before treatment (P>0.05). After 6 months of treatment, the quality of life in the observation group was higher than that in the control group (P<0.05). [a]*P*<0.05; compared with before treatment, [b]*P*<0.05.

Table 4. Comparison of drug safety between the two groups [n (%)]

Grouping	Cases	Infection	Gastrointestinal discomfort	Abnormal blood pressure	Abnormal liver and kidney function	Dizziness and drowsiness	Rate
Observation group	34	0 (0.00)	1 (2.94)	0 (0.00)	1 (2.94)	1 (2.94)	3 (8.82)
Control group	34	1 (2.94)	0 (0.00)	1 (2.94)	1 (2.94)	2 (5.88)	5 (14.71)
x^2	/						5.451
P	/						0.033

Comparison of drug safety between the two groups

There was no significant difference in the incidence of infection, gastrointestinal discomfort, abnormal blood pressure, abnormal liver and kidney function and dizziness and drowsiness between the two groups during the treatment (**Table 4**, *P*>0.05).

Discussion

TAO is a common orbital disease, and its pathogenesis is generally believed to be related to organ immunodeficiency. The clinical manifestations of TAO are eyelid swelling, protruding eyeballs, and conjunctival lesions, which affect patients' vision and quality of life [20]. Medication therapy, radiation therapy, and surgical treatment are common interventions in TAO patients, and there are no standard treatments [21]. Prednisone oral tablets contained glucocorticoids, which can inhibit connective tissue proliferation and reduce capillary permeability, inflammatory factors, immunosuppression and inflammatory cell infiltration [22]. Studies [23] have shown that glucocorticoids can inhibit the release of immune active cells and exert good therapeutic effects on TAO patients. However, long-term use of high-dose glucocorticoids is prone to increase systemic allergic reactions,

and some patients can develop symptoms such as shortness of breath and chest tightness, and patients have a high recurrence rate after drug withdrawal, leading to limitations in its clinical use [24].

HHT has been used in treatment of TAO patients with satisfactory efficacy [25]. Glucocorticoids have anti-inflammatory and immunomodulatory effects in TAO patients, and can affect the body's protein and electrolyte metabolism. Clinical studies have shown that high-doses glucocorticoids have anti-inflammatory effects, which can maintain and stabilize the capillary wall, and reduce cell infiltration. Studies [26] have demonstrated that HHT can play an anti-inflammatory and immunomodulatory role in patients with TAO, and can also inhibit peripheral conversion of T4 to T3, which is an important component of management. Studies [27] also found that the effect of intravenous administration of glucocorticoids is better than oral/local injection, with fewer adverse drug reactions and high safety. In this study, methylprednisolone injection was intravenously given, and then prednisone acetate tablets were taken orally, yielding good therapeutic effects. By combining with the corresponding receptors of target tissue cells in the eye orbit, the drug can inhibit release from immunocompetent cells, thereby decreasing the synthesis of fibroblasts in the orbit and improving the patient's vision [28]. In this study, the visual acuity of the observation group at 1, 3 and 6 months was higher than that of the control group ($P<0.05$), indicating that glucocorticoid-based HHT can improve the visual acuity in patients with TAO.

On the other hand, glucocorticoids can reduce the congestion and edema of the soft tissues around the eyeball, reduce the orbital pressure, and help improve the ocular surface circulation, which can stabilize the patient's condition and facilitate the patient's recovery. In this study, the levels of TMH, BUT, and SIt in the observation group were higher than those in the control group ($P<0.05$). The levels of R-scan and FS in the observation group were lower than those in the control group ($P<0.05$). The quality of life scores of the observation group were higher than those of the control group at 6 months after treatment ($P<0.05$). These indicated that HHT can improve the ocular surface microenvironment as well as the quality of life. Modern pharmacological results show that hormonal drugs can inhibit the formation of inflammatory corneal neovascularization at the ocular surface during the treatment of HHT, which can stabilize the permeability of blood vessels and the blood-aqueous barrier, thereby inhibiting the original fibrin exudation.

Studies [29] have shown that hormone HHT can rapidly alleviate the patient's condition and delay its deterioration in TAO patients. Studies also found that HHT are likely to cause dysfunction of metabolic functions due to high doses of use in a short time, resulting in electrolyte disturbances, infections, high blood sugar and rapid heartbeat, *etc*., resulting in poor treatment tolerance and compliance. In this study, the incidence of adverse reactions was not statistically significant ($P>0.05$), indicating a high safety of HHT in patients with TAO. However, the indications such as HHT and electrolytes levels should be monitored in the course of medication, and effective measures should be taken in real time to consolidate clinical treatment effect.

In summary, HHT can provide good short-term efficacy in patients with TAO and improve the patient's vision, ocular surface environment as well as quality of life after treatment, without increasing the incidence of adverse reactions.

Disclosure of conflict of interest

None.

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