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# Treatment using Western medicine and traditional Chinese medicine in hormone-dependent myasthenia gravis

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**Objective:** The aim of this study was to observe the therapeutic effect of integrative Chinese and Western medicine (ICWM) and single Western medicine approaches in treating patients with myasthenia gravis and summarize remedial before and after changes in acetylcholine receptor content and attenuation of repetitive nerve stimulation of electromyography of the two groups. **Methods:** The Western medicine group included 18 patients treated with prednisone, and the ICWM group included 50 patients treated with Chinese traditional medicine, Zhongjiling, which has the therapeutic principle of 'warming and coordinating Qi yang and supporting Zhenyuan.' The period of treatment was 3 months. **Results:** In the ICWM group, the cure rate was 10%, elementary rate was 18%, appearing effect rate was 42% and the total effective rate was 92%. In the Western medicine group, the rates were 6.3, 10.4, 20.8 and 77.1%, respectively. In the ICWM group, 14 patients were withdrawn from prednisone treatment (28%), 36 patients had their prednisone dose reduced (72%) and the total rate was 100%. In the Western medicine group, the rates were 0, 93.7 and 93.7%, respectively. In the ICWM group, the side-effect rate was 4% and the recrudescence rate was 2%. In the Western medicine group, the rates were 18.8 and 14.6%, respectively. **Conclusion:** The ICWM approach appeared to be more effective than single Western medicine in treating myasthenia gravis patients. This approach not only had a distinct curative effect, but prednisone could also be reduced or withdrawn and hormonal side effects and recrudescence rates were decreased.

Myasthenia gravis (MG), an autoimmune disease, has the combined effect of acetylcholine receptor antibody (AChRab)-mediated and cell-mediated immunity dependence and, in addition, mainly involves the acetylcholine receptor (AChR) on the postsynaptic membrane at the neuromuscular junction. MG is one of the most frequently stubborn diseases in neurology, with an incidence rate of 0.5–5/100,000 people each year [1]. Hormone-dependent MG refers to those patients who are sensitive to glucocorticoids and recur after reduction or withdrawal of treatment. Such cases have been formidable in clinical treatment. Recently, we treated 50 patients with MG by a new method – using integrated traditional Chinese medicine and Western medicine (ICWM), which had a distinct curative effect. Concurrently, we performed a random, double-blind comparison of the effect with a single Western medicine (WM) group of 48 MG patients.

hormone therapy. We randomly divided the patients into two groups: an ICWM and WM group. In the ICWM group, there were 22 males and 28 females aged 19–58 years, and the average age was approximately  $37.8 \pm 3.7$  years. The 48 WM patients were composed of 23 males and 25 females aged 20–57 years, with an average age of approximately  $38.2 \pm 3.9$  years (Tables 1–3).

## Clinical symptoms

All of the patients had the same typical MG symptoms, which abate in the morning or after resting and aggravate in the evening or after exertion. A neostigmine test proved positive if: with repeated low frequency electric stimulating (1–10 Hz, USU 3 Hz), the amplitude of muscular action potential dropped rapidly by over 10%; Sero-AChRab was positive; fatigue test was positive; single-fiber electromyography [EMG] was positive; and prolongation or blockage of excitation conduction could be observed. The value of adjacent electric potential difference was prolonged for all patients (Table 4).

## Clinical classification

According to the modified Osserman clinical classification, patients are classified as shown in Table 5.

## Clinical documents

### Patient information

All 98 patients were being treated for MG at the MG Department of Yiling Hospital, China. All had recurrent history after reducing hormone therapy and an indication for the application of

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Therapeutic methods

*ICWM group*

Patients in the ICWM group were administered prednisone (1 mg/kg) every morning and 5 g of Zhongjiling with water three times a day after meals (drug product of Hebei Yiling Medical Group).

*WM group*

Besides prednisone, the patients took 5 g of placebo with water three times a day after meals. The placebo, made of parched starch, is similar to Zhongjiling in form and color (provided by Hebei Yiling Medical Group).

*Period of treatment*

A treatment period of 3 months was observed, during which time, no additional treatments were administered. Under the premise that the symptoms are ameliorated and the patients are in a stable condition, prednisone can be gradually reduced or withdrawn, which is then recorded.

Criteria for evaluation of effectiveness

Box 1 shows the relative record equation according to Xu Xianhao and other experts' rating methods of clinical effectiveness for MG patients [2]. The following evaluation criteria is drafted:

- Cure: clinical relative score of at least 95%;
- Elementary cure: clinical relative score of 80–95%;
- Excellent: clinical relative score of 50–80%;
- Improved: clinical relative score of 25–50%;
- Ineffective: clinical relative score of 25% or less.

Therapeutic efficacy & analysis

*Analysis of curative effect*

Clinical observation focused mainly on the amelioration of the function of ocular muscles, masticatory muscles, facial muscles, respiratory muscles, trunk and extremities. It was found that the cure rate in the ICWM group was 10%, the elementary rate was 18%, the appearing effect rate was 42% and the total effective rate was 92%. In the WM group, the rates were 6.3, 10.4, 39.6 and 85.5%, respectively (Table 6).

*Analysis of before & after changes of AChRAB*

AChRAB was detected using enzyme-linked immunosorbent assay (ELISA) and both groups proved positive. The level of AChRAB was found to be decreased following treatment and a number proved negative (Table 7).

*Analysis of before & after changes of electromyography*

The patients' left orbicular muscle, deltoid muscle and left abductor digiti minimi was analyzed with CANPAPAPM EMG (Denmark). Every patient was checked identically before and after. In addition, they received three doses of repeated low frequency electric stimulation with a 10-min interval. The attenuation percent of action potential was calculated and an average value recorded (Table 8).

*Analysis of reduction & withdrawal of prednisone after treatment*

In order to have an external understanding of patients' conditions, we observed in detail when we reduced and withdrew prednisone under the premise of stable conditions. In the ICWM group, 14 patients were withdrawn from prednisone (28%), 36 patients had prednisone reduced (72%) and the total rate was 100%. In the WM group, the rates were 0, 93.7 and 93.7%, respectively (Table 9).

*Contrast of incidence rate of untoward hormone reaction*

The following untoward reactions appeared after the application of hormone: Cushing's syndrome (moon-shaped face, buffalo hump, purple striae, hairiness and acne), infection, Cushing ulcer, mental subnormality, myopathy, myalgia, steroid diabetes and hypopotassemia. In the ICWM group, two patients (4%) had only low-grade prosopo-acne; in the WM group, nine out of 48 patients (18.8%) had untoward reaction, three had a single untoward reaction and six had more than two untoward reactions. The incidence rate in the ICWM group was much lower than that in the WM group (statistical analysis:  $\chi^2 = 4.33$ ;  $p < 0.05$ ).

*Contrast of relapse rate*

Only one patient (2.0%) in the ICWM group relapsed once in 3 months after the elimination of the symptoms due to upper respiratory tract infection, yet was relieved after prompt control. In the WM group, seven patients (14.6%) relapsed many times during reduction, three

**Box 1. Relative record equation.**

$$\text{Relative record} = \frac{\left( \text{score of cardinal symptom pretreatment} - \left( \text{score of cardinal symptom post-treatment} \right) \right)}{\text{score of cardinal symptom post-treatment}}$$

were in the ineffective range, another three were basically relieved and one was partially relieved. The relapse rate in the ICWM group was much lower than that in the WM group ( $\chi^2 = 5.59$ ;  $p < 0.05$ ).

#### Results & conclusions

The results of this clinical study provide the detailed figures that, in the ICWM group, the cure rate was 10%, elementary rate was 18%, appearing effect rate was 42% and total effective rate was 92%. In the WM group, the rates were 6.3, 10.4, 20.8 and 77.1%, respectively. In the ICWM group, 14 patients were withdrawn from prednisone (28%), 36 patients had prednisone reduced (72%) and the total rate was 100%. In the WM group, the rates were 0, 93.7 and 93.7%, respectively. In the ICWM group, the side-effect rate was 4% and the recrudescence rate was 2%. In the WM group, the rates were 18.8 ( $\chi^2 = 4.33$ ;  $p < 0.05$ ) and 14.6% ( $\chi^2 = 5.59$ ;  $p < 0.05$ ), respectively. This demonstrates that the ICWM approach was better than the single WM approach in treating MG patients. This approach not only had a distinct curative effect, but prednisone could also be reduced or withdrawn and the hormonal side effect and recrudescence rates decreased.

Wu Yiling, after many years' clinical research on the relationship between Qijing (extra meridian) and the pathogenesis of MG immunology, discovered that the conduction disturbance of MG neurotransmitter resembles the delinquency of channel qi, moves in the meridians and the blockage is caused by the malfunction of meridians. The function of Qijing to adjust qi and blood, together with the malfunction of superficial venules to disseminate qi and blood, will directly reverse qi and blood. Therefore, Wu broke through the traditional methods and put forward a new method of analyzing under the theory of Qijing and meridian. He believed that the cause of MG was 'the deficiency of Qijing and decadence of primordial qi', and 'the deficiency and blockage of the meridian qi' was its main patho-element. Under the therapeutic principle of 'warming and coordinating Qi yang, supporting Zhenyuan, dredging meridians and activating collaterals', he use many Chinese herbs, such as Yinyanghuo, Ziheche, Huangqi, Baizhu, Fuling and Danggui to make a pure Chinese drug – Zhongjiling. All of these herbs have the therapeutic principle of 'smoothing Qijing, smoothing eight extra meridians, supporting Zhenyuan and filling Zhenjing'.

Zhongjiling can brim Qiyang, recover primordial energy and cure the symptoms of ptosis and myasthenia of limbs.

Modern pharmacological research discovered that the Chinese herb Yinyanghuo enhances the secretion of thalamus–hypophysis–gonad, adrenal cortex and thymus; Ziheche stimulates the adrenal cortex; Baizhu can improve deglutition of the reticuloendothelial system, raise the conversion rate of lymphocyte and enhance disease resistance; Danggui can clear free radicals in the serum, promote nonspecific immunity and activate the complement system, it can also enhance immunity to inhibition caused by cortical hormone; Fuling can regulate immunity, protect the liver, lower enzymes, resist viruses indirectly and activate the biological activity of interferon and leukoregulin; Huangqi sharply promotes deglutition of the reticuloendothelial system when it is inhibited by hormones [6] and can improve the immunological function of cells and body fluid, enhance the activity of natural killer cells and stimulate the formation of interferon. In brief, these herbs regulate the immune system, giving them a better distinct curative effect over MG, thus they deserve further development and application.

#### Discussion

MG is considered to be a type of autoimmune disease. Prednisone is the first drug treatment of choice. Its mechanism of action is to inhibit the synthesis of AChRab and ensure the AChR on the postsynaptic membrane at the neuromuscular junction is lesser or not destroyed by the autoimmune system, while enabling the proptosis frontal membrane to release ACh in order to cause stimulation. The main reason why prednisone can cure MG is as a result of its power to retrieve the abnormal immunological function of thymus, to inhibit the formation of the thymus germinal center, to improve the immunological function of lymphocyte (which is adjusted by thymus), to inhibit the formation of AChRab in serum and to stimulate the release of ACh at neuromuscular junctions to improve the function of transmission [3]. It is reported that some side effects occurred during the application of hormone therapy, such as hypertension, diabetes, Cushing's syndrome, aseptic necroses of femoral head and pathological fracture [4,5]. During the course of reducing the hormone, the symptoms relapsed frequently owing to the rapid speed, and even caused myasthenia. Therefore, the exploration and development of new practical drugs with fewer side effects is urgently required.

**Table 1. Age distribution of the two patient groups.**

Group	n	Age (years, %)				
		≤20	21-30	31-40	41-50	51-60
ICWM	50	4 (8%)	11 (22.9%)	17 (34%)	13 (26%)	5 (10%)
WM	48	3 (6.3%)	12 (25%)	15 (31.3%)	14 (29.2%)	4 (8.3%)

Results of statistical analysis:  $\chi^2 = 0.42$ ;  $p > 0.05$ ; There was no significant difference in age distribution.  
 ICWM: Integrative Chinese and Western medicine; WM: Western medicine.

**Table 2. Predisposing factor of the two patient groups.**

Group	n	Fatigue	URI	Enterogastritis	Decrement & withdrawal of cholinesterase inhibitor	Unknown
ICWM	50	12 (24%)	15 (30%)	4 (8%)	11 (22%)	3 (6%)
WM	48	11 (22.9%)	16 (33.3%)	10 (20.8%)	9 (18.8%)	2 (4.2%)

Results of statistical analysis:  $\chi^2 = 2.95$ ;  $p > 0.05$ ; There was no significant difference in predisposing factors.  
 ICWM: Integrative Chinese and Western medicine; URI: Upper respiratory infection; WM: Western medicine.

**Table 3. Main complications of the two patient groups.**

Group	n	Thymoma postop.	Thymic hyperplasia	Hyperthyroidism	Diabetes	Amyotrophy
ICWM	19	4 (21.1%)	7 (36.9%)	3 (15.8%)	2 (10.5%)	3 (15.8%)
WM	18	3 (16.7%)	5 (27.8%)	3 (16.7%)	3 (16.7%)	4 (22.2%)

Results of statistical analysis:  $\chi^2 = 0.79$ ;  $p > 0.05$ ; There was no significant difference in deuteropathy.  
 ICWM: Integrative Chinese and Western medicine; Postop.: Postoperatively; WM: Western medicine.

**Table 4. The course of disease distribution of the two patient groups.**

Group	n	≤1 year	~5 years	~10 years	~20 years	>20 years
ICWM	50	7 (14%)	11 (22%)	13 (26%)	12 (24%)	7 (14%)
WM	48	6 (12.5%)	10 (20.8%)	15 (31.3%)	11 (22.9%)	6 (12.5%)

Results of statistical analysis:  $\chi^2 = 0.35$ ;  $p > 0.05$ ; There was no significant difference in distribution of the course of disease.  
 ICWM: Integrative Chinese and Western medicine; URI: Upper respiratory infection; WM: Western medicine.

**Table 5. Clinical classification of the two patient groups.**

Group	n	I	IIA	IIB	III	IV	V
ICWM	50	17 (34%)	13 (26%)	9 (18%)	4 (8%)	4 (8%)	3 (6%)
WM	48	16 (33.3%)	12 (25%)	10 (20.8%)	3 (6.3%)	5b (10.4%)	2b (4.2%)

Results of statistical analysis:  $\chi^2 = 0.54$ ;  $p > 0.05$ ; There was no significant difference in clinical classification.  
 ICWM: Integrative Chinese and Western medicine; WM: Western medicine.

**Table 6. The curative effect statistics of the two patient groups.**

Group	n	Cure	Elementary cure	Excellent	Improved	Ineffective	Total
ICWM	50	5 (10%)	9 (18%)	21 (42%)	11 (22%)	4 (8%)	46 (92%)
WM	48	3 (6.3%)	5 (10.4%)	10 (20.8%)	19 (39.6%)	11 (22.9%)	37 (77.1%)

Results of ridit analysis:  $u = 2.84$ ;  $p < 0.01$ ; A significant difference in clinical classification was observed.  
 ICWM: Integrative Chinese and Western medicine; WM: Western medicine.

**Table 7. Before and after changes of AChRAB of the two patient groups.**

Group	n	Prior-treatment ± SD	Post-treatment ± SD	Difference value ± SD	t	p-value
ICWM	50	0.59 ± 0.21	0.37 ± 0.21	0.22 ± 0.19	5.24	<0.01
WM	48	0.62 ± 0.22	0.41 ± 0.20	0.21 ± 0.21	4.89	<0.01

Results of statistical analysis: comparison of the difference  $t = 0.25$ ;  $p = 0.05$ ; There was no significant difference in changes of AChRAB.

ICWM: Integrative Chinese and Western medicine; SD: Standard deviation; WM: Western medicine.

**Table 8. Analysis of before and after electromyography of the two patient groups.**

Region	Group	n	Pre-treatment ± SD	Post-treatment ± SD	Difference value ± SD	t	p-value
Orbicular muscle	ICWM	50	21.67 ± 18.35	10.65 ± 7.99	11.02 ± 9.02	7.39	<0.01
	WM	48	22.32 ± 19.41	11.75 ± 8.13	10.57 ± 9.39	3.89	<0.01
Deltoid muscle	ICWM	50	27.74 ± 13.04	14.98 ± 14.25	12.76 ± 11.32	8.86	<0.01
	WM	48	28.91 ± 14.81	15.02 ± 15.31	13.89 ± 11.84	5.05	0<.01
Abductor digiti minimi	ICWM	50	14.66 ± 12.14	8.28 ± 8.16	6.38 ± 5.74	5.85	<0.01
	WM	48	17.87 ± 13.06	9.32 ± 9.07	8.55 ± 7.13	4.17	<0.01

Results of statistical analysis: comparison of the difference of before and after EMG, orbicular muscle  $t = 0.33$ ;  $p < 0.01$ ; deltoid muscle  $t = 0.66$ ;  $p < 0.01$ ; abductor digiti minimi  $t = 2.38$ ;  $p < 0.01$ ; significant difference in the attenuation of before and after EMG can be observed.

EMG: Electromyography; ICWM: Integrative Chinese and Western medicine; WM: Western medicine.

**Table 9. Reduction and withdrawal of prednisone in the two patient groups.**

Group	n	Withdrawal	Reduced by half or more	Reduced by a quarter or more	Reduced by a quarter or less	Remain	Total rate
ICWM	50	14 (28%)	19 (38%)	11 (22%)	6 (12%)	0 (0%)	100%
WM	48	0 (0%)	12 (25%)	17 (35.4%)	16 (33.3%)	3 (6.3%)	93.7%

Results of statistical analysis: ridit test:  $u = 4.56$ ;  $p < 0.01$ ; a significant difference between two groups was observed; This indicated that the ICWM group relied much less on prednisone than the WM group if the conditions were stable.

ICWM: Integrative Chinese and Western medicine; WM: Western medicine.

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