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Application of Chaihu-Guizhi-Longgu-Muli decoction combined with Liuwei Dihuang Pills in the treatment of menopausal insomnia and its effect on sleep quality

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Abstract: To explore the application of Chaihu-Guizhi-Longgu-Muli decoction (CGLM) combined with Liuwei Dihuang Pills in the treatment of menopausal insomnia and its effect on sleep quality. The data of 120 menopausal insomnia patients admitted to our hospital from February 2019 to February 2020 were retrospectively analyzed and they were equally divided into the experimental group (n=60) and the control group (n=60) according to the order of admission. All patients were treated with Liuwei Dihuang Pills, and the experimental group was additionally given CGLM. The Pittsburgh Sleep Quality Index (PSQI), estrogen level, negative emotion score, quality of life score, serum β-endorphin (β-EP) level, serotonin level (5-HT) and treatment effective rate were compared between the two groups of patients. After treatment, the experimental group obtained markedly lower PSQI scores and negative emotion scores than the control group (P<0.001). The estrogen levels, β-EP levels and 5-HT levels of the experimental group after treatment were significantly better than those of the control group (P<0.001). Higher quality of life scores and treatment effective rates were observed in the experimental group after treatment than the control group (P<0.001). CGLM combined with Liuwei Dihuang Pills can regulate the serum hormone levels of patients with menopausal insomnia, reduce negative emotions and improve sleep quality and quality of life, which merits clinical promotion.

Keywords: Chaihu-Guizhi-Longgu-Muli decoction, Liuwei Dihuang Pills, enopausal insomnia patients.

INTRODUCTION

Perimenopausal women usually experience changes in the level of sex hormones due to ovarian hypofunction, resulting in a series of mental and physical symptoms, which are clinically referred to as menopausal syndrome (Semenova *et al.*, 2019). Insomnia is one of the most frequent symptoms of menopausal syndrome (Delamater *et al.*, 2018), which gives rise to difficulty falling asleep and negative emotions such as anxiety and depression due to poor sleep quality. In severe cases, impairment in immune function may also occur, resulting in underlying diseases (Garcia *et al.*, 2018; Yoshimura *et al.*, 2018). Currently, hormone replacement therapy is mainly applied in Western medicine for the treatment of menopausal insomnia; however, the uncertainty of its efficacy fails to ensure rapid recovery, and toxic side effects of nerve block have been identified in some previous studies (Rémi *et al.*, 2019; Cukor *et al.*, 2021). Recent studies are unequivocal about the efficacy of the holistic treatment and syndrome differentiation of traditional Chinese medicine (TCM) on menopausal syndromes. Liuwei Dihuang Pills, which are composed of Rehmannia glutinosa, Moutan cortex and Chinese yam, can effectively regulate the hormone secretion of patients and alleviate their clinical symptoms (Otaka *et al.*, 2019; Ozcan *et al.*, 2017). Moreover, some studies applied Chaihu-Guizhi-Longgu-Muli decoction (CGLM) to patients with anxiety insomnia, severe depression and insomnia, and found significantly improved sleep quality and quality of life of the patients (Kim *et al.*, 2020; Khanna *et al.*, 2020; Yang *et al.*, 2020), indicating that CGLM yields the effects of eliminating negative emotions by relieving heat, soothing the nerves and calming the mind. Nonetheless, the therapeutic effect of CGLM on patients with menopausal insomnia has yet been discussed. The current study was designed to explore the clinical efficacy of CGLM plus Liuwei Dihuang Pills in menopausal insomnia patients and it's influence on menopausal sleep quality.

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MATERIALS AND METHODS

Research design

This study is a retrospective study, conducted in our hospital from February 2019 to February 2020, with an aim to evaluate the application of CGLM combined with Liuwei Dihuang Pills in the treatment of menopausal insomnia and its effect on sleep quality.

Recruitment of research subjects

The data of menopausal insomnia patients admitted to our hospital from February 2019 to February 2020 were retrospectively analyzed, and the patients were included according to the following criteria: (1) The patients met the diagnostic criteria in NICE's "Diagnosis and

Management of Menopause" (Lumsden, 2016), and were accompanied by various degrees of abnormal mood, anxiety, hyperhidrosis, insomnia and other menopausal symptoms; (2) The patients had amenorrhea more than 6 months due to natural causes; (3) The patients had no organic disease after examination, with normal results of breast examination, cervical smear and B-ultrasound; (4) With complete clinical data. Exclusion criteria: (1) With mental problems or inability for communication; (2) With other organic diseases; (3) Use of sex hormone drugs in the past 1 year; (4) With vaginal bleeding; (5) Did not meet the diagnostic criteria; (6) With sleep problems caused by environmental factors such as tea drinking, and diet; (7) With incomplete clinical data; (8) Withdrawal from treatment midway.

Inclusion procedures

A total of 120 patients were enrolled in this study and were equally divided into the experimental group (n=60) and the control group (n=60) according to the order of admission. After enrollment, the socio-demographic data and clinical performance data of the patients were collected. After analysis, it was found that there was no statistical difference in general information between the two groups (P>0.05), as shown in table 1.

Moral considerations

This study complied with the principles of the Declaration of Helsinki (World Medical Association, 2016) and was approved by the review committee of the hospital's ethical review institution. The patients signed the informed consent form after being fully informed of the purpose, significance, content, and confidentiality of the research.

Withdrawal criteria

If the patients had the following situations and were judged by the research team to be not suitable for the further experiment, their case records were preserved only without data analysis: (1) With adverse events or serious adverse events; (2) The condition deteriorated during the experiment; (3) With serious complications; (4) The patients were unwilling to continue the clinical trial midway and requested for withdrawal.

Methods

All patients were given routine treatment, and diet and exercise programs were formulated according to their actual conditions to maintain a regular daily schedule. The patient took Liuwei Dihuang Pills (Baoding Chinese Medicine Pharmaceutical Co., Ltd., NMPA approval number Z13022425) three times a day, 8 pills each time for a total of 3 months. The experimental group was additionally treated with CGLM. CGLM contains 15g each of Bupleurum, Scutellaria, Guizhi, Codonopsis, Ginseng, and Yejiao Teng, 35g each of raw keel and raw oyster, 10g each of Poria and Pinellia, rhubarb 5g, wild jujube seed 25g and ginger 2g. Add 1200ml of the above ingredients to water and extract 400mL of liquid. U Take the liquid with warm water in the morning and before going to bed. All patients were treated for 3 months.

Observational criteria

(1) General information: number of patients, name, age, course of disease, average body weight, BMI, comorbidities, marital status, place of residence, monthly income, living habits and education level.

(2) The Pittsburgh Sleep Quality Index (PSQI): PSQI (Mollayeva *et al.*, 2016) is one of the most widely used sleep quality assessment scales in clinical applications, and its credibility and sensitivity have been confirmed by a substantial amount of literature. The scale was used to evaluate the patient's sleep quality in the last month. It consists of 19 self-evaluated items and 5 other-evaluated items. With the 19th self-evaluated item and 5 other-evaluated items excluded from scoring, the remaining 18 items consist of 7 components, namely, sleep quality, sleep latency, sleep duration, sleep efficacy, sleep disorders, hypnotic drugs and day dysfunction. The score of each component is between 0-3 points, and the total score is 0-21 points. The lower the score, the better the patient's sleep quality. The PSQI scores of patients after 3 months of treatment (T3) were compared.

(3) Estrogen level: Before treatment (T1), 1 month after treatment (T2), and 3 months after treatment (T3), 5 ml of fasting venous blood was drawn from the patients, rested for 0.5 h, and centrifuged at 3000 r/min to obtain serum. Immunoradioanalysis (Tianjin Jiuding Medical Bioengineering Co., Ltd., Immunoradioanalysis Kit, S20083117) was used to determine serum estradiol and prolactin levels.

(4) Negative emotion score: Hospital Anxiety and Depression Scale (HAD) (Serpytis *et al.*, 2018) is one of the most widely used negative emotion rating scales in clinical application, and its credibility and sensitivity have been confirmed by a substantial amount of literature. The scale is divided into anxiety (HAD-A) scoring scale and depression (HAD-D) scoring scale, with the scores of the two scales between 0-15 points. The higher the score, the more serious the anxiety and depression. The HAD scores of patients at T1 and T3 were compared.

(5) Quality of life score: Generic Quality of Life Inventory -74 (GQOLI-74) (Olsson *et al.*, 2019) is one of the most widely used clinical quality of life assessment scales. The scale contains four scoring factors: Mental function, physical function, social function and material life state, with a total score of 100 points. The GQOLI-74 scores of patients at T3 were compared.

(6) β-EP level and 5-HT level: 6 ml of fasting venous blood was collected from the patients at T1, T2 and T3.

The levels of β-EP and 5-HT were determined by enzyme-linked immunosorbent assay (Beijing Kewei Clinical Diagnostic Reagent Co., Ltd., enzyme-linked immunosorbent kit, S20060028).

(7) Treatment effective rate: Cured: The patient's clinical symptoms have basically disappeared and the sleep duration of the whole night lasted more than 6 hours. Markedly effective: the patient's symptoms have been significantly improved, and the sleep duration throughout the night has increased by more than 3 hours. Effective: The patient's clinical symptoms have been relieved, and the sleep time throughout the night has increased by less than 3 hours. Ineffective: No improvement in sleep quality.

STATISTICAL ANALYSES

The data processing software selected in this research was SPSS20.0, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used to plot the graphics. The counting data adopted the x2 test and was expressed by [n(%)], and the measurement data were expressed by ($\bar{x}$±s) and analyzed by t-test. P<0.05 indicates that the difference is statistically significant.

RESULTS

Comparison of general information

The two groups had no significant difference in general information (P>0.05). See table 1.

Comparison of PSQI

Lower PSQI scores were obtained in the experimental group after treatment, as compared to the control group (P<0.001). See table 2.

Comparison of estrogen levels

The level of estrogen in the experimental group after treatment was remarkably better than that in the control group (P<0.001), as shown in fig. 1.

Comparison of negative emotion scores

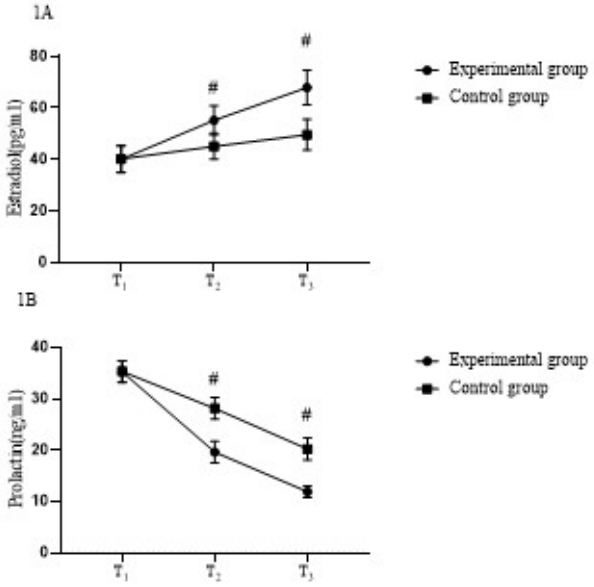
The experimental group yielded a better outcome in terms of negative emotion scores than the control group (P<0.001). See fig. 2.

Comparison of quality of life scores

Higher quality of life scores of patients in the experimental group after treatment than those in the control group were observed (P<0.001), as shown in table 3.

Comparison of β-EP level and 5-HT level

The experimental group had better β-EP and 5-HT levels than the control group after treatment (P<0.001), as shown in fig. 3.



Note: The horizontal axis in fig. 1 from left to right is before treatment (T1), 1month after treatment (T2) and 3 months after treatment (T3). The dotted line in the figure is group A and the square line is group B; # indicates P<0.001.

Fig. 1A is estradiol. There was no statistical difference in the estradiol of T1 between the experimental group and the control group (40.11±5.21 vs 40.23±5.10, P>0.05). The estradiol levels of T2 and T3 in the experimental group were significantly higher than those in the control group (55.24±5.68 vs 45.12±5.10, 67.95±6.68 vs 49.65±5.98, P<0.001).

Fig. 1B shows prolactin. There was no statistical difference between the experimental group and the control group in T1 prolactin (35.26±2.15 vs 35.33±2.10, P>0.05). The prolactin of the experimental group at T2 and T3 was significantly lower than that of the control group (19.62±2.10 vs 28.11±2.10, 11.92±1.10 vs 20.23±2.12, P<0.001).

Fig. 1: Comparison of estrogen levels (x±s)

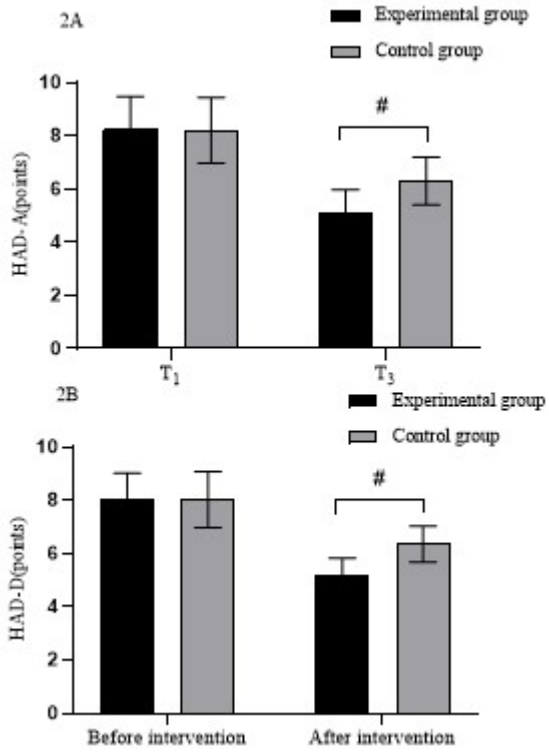
Comparison of treatment effective rate

The total effective rate of treatment in the experimental group was markedly higher than that in the control group (P<0.001). See table 4.

DISCUSSION

Perimenopausal hypothalamic-pituitary-gonadal axis feedback dysfunction leads to decreased ovarian hormone secretion and neurological disorders, resulting in a cascade of symptoms such as sexual dysfunction, emotional instability, and insomnia, among which insomnia is the most common clinical symptom (Kalmbach *et al.*, 2020). This symptom takes a toll on patients' physical health, intensifies patients' psychological pressure and impairs their quality of life. In TCM, menopausal insomnia is categorized as "sleep disorders due to malaise" as it is believed that sleep is dominated by the state of mind (Martucci *et al.*, 2020). Specifically, during perimenopause, the debility of thoroughfare and conception vessels and kidney-Qi

deficiency lead to emotional depression, triggering internal injuries of the body and sleep disorders, in which the heart and kidney non-interaction is one of the important syndromes.

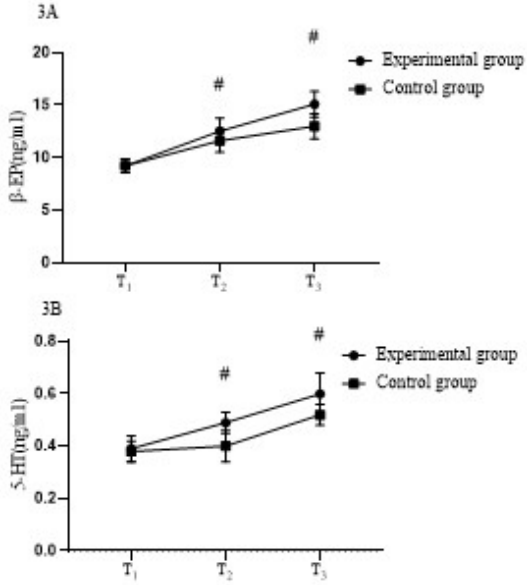


Note: Fig. 2A is the HAD-A score and fig. 2B is the HAD-D score; the horizontal axes of the two figures from left to right are before treatment (T1) and 3 months after treatment (T3); the black area in the figure is the experimental group, The gray area is the control group; # indicates P<0.001.

The HAD-A score and HAD-D score of T1 between the experimental group and the control group were not statistically different (8.23±1.25 vs 8.20±1.24, 8.00±1.01 vs 8.02±1.06, P>0.05); the HAD-A score at T3 in the experimental group The HAD-D score was significantly lower than that of the control group (5.10±0.87 vs 6.30±0.89, 5.15±0.68 vs 6.35±0.67, P<0.001).

Fig. 2: Comparison of negative emotion scores (x±s, points)

It indicates the incoordination between the two viscera, resulting in negative emotions and an overstrung state of patients, which consequently highlights the importance of improving the state of mind in treatment. The CGLM selected in this study originates from "Treatise on Febrile Diseases and Miscellaneous Diseases", which has been reported to yield a promising therapeutic effect in depression, anxiety, insomnia, and other emotion-related diseases (Yu *et al.*, 2017). Song *et al.* believe that regardless of the cause of insomnia, the basic etiology in TCM is nutrient-defense disharmony, which therefore underlines the regulation of Yin and Yang as the key to the treatment of insomnia (Song *et al.*, 2020). Accordingly, they treated patients with anxiety insomnia with CGLM and found that the sleep disorder score of the observation group after treatment was (15.72 ± 4.10) points, which was significantly lower than that of the control group (P<0.001), indicating that CGLM can reconcile Yin and Yang, eliminate negative emotions, and help alleviate the insomnia symptoms of patients. It is consistent with the results of this study that the PSQI score of the experimental group after treatment was significantly lower than that of the control group (P<0.001).



Note: The horizontal axis in fig. 3 from left to right is before treatment (T1), 1 month after treatment (T2), and 3 months after treatment (T3). The dotted line in the figure is the experimental group, and the square line is the control group; # indicates P<0.001.

Fig. 3A shows the β-EP level. There was no statistical difference in the β-EP level at T1 between the experimental group and the control group (9.23±0.65 vs 9.24±0.67, P>0.05); the β-EP level at T2 and T3 in the experimental group was significantly higher than the control group (12.54±1.23 vs 11.62±1.10, 15.10±1.22 vs 13.00±1.20, P<0.001).

Fig. 3B shows the 5-HT level. The 5-HT levels at T1 in the experimental group and the control group were not statistically different (0.39±0.05 vs 0.38±0.04, P>0.05); the 5-HT levels at T2 and T3 in the experimental group were significantly higher than the control group (0.49±0.04 vs 0.40±0.06, 0.60±0.08 vs 0.52±0.04, P<0.001).

Fig. 3: Comparison of β-EP levels and 5-HT levels in patients ($\bar{x}$±s, ng/ml)

In addition, this study found that the estrogen levels of the two groups of patients were significantly improved after treatment. It is speculated that Liuwei Dihuang Pills, containing Rehmannia glutinosa, Cornus, Moutan bark, Chinese yam, Poria cocos, can exert a positive Yin nourishing effect and can regulate the level of hormone secretion in patients, to mitigate symptoms such as kidney deficiency and sexual dysfunction.

Table 1: Comparison of general information

Groups	Experimental group (n=60)	Control group (n=60)	X^2/t	P
Age (year)				
Range	48-64	47-60		
Average age	55.23±2.15	55.24±2.10	0.026	0.980
Average weight (kg)	54.21±2.12	54.23±2.24	0.050	0.960
BMI (kg/m^2)	21.22±2.10	21.23±2.11	0.026	0.979
Course of disease (year)	4.68±1.01	4.74±1.03	0.322	0.748
Comorbidities				
Depression	8	9	0.069	0.793
Anxiety	12	11	0.054	0.817
Hypertension	15	16	0.044	0.835
Diabetes	10	12	0.223	0.637
Lung disease	5	4	0.120	0.729
Marital status			0.324	0.570
Married	52	54		
Unmarried, divorced, widowed	8	6		
Place of residence			0.134	0.715
Urban	30	32		
Rural	30	28		
Monthly income (yuan)			0.137	0.711
≥4000	24	26		
<4000	36	34		
Living habits				
Smoking history	15	18	0.376	0.540
Drinking history	20	18	0.154	0.695
Education level			0.137	0.711
High school and below	24	26		
University and above	36	34		

Table 2: Comparison of PSQI after treatment (x±s)

Groups	Sleep quality	Sleep latency	Sleep duration	Sleep efficacy	Sleep disorders	Hypnotic drugs	Day dysfunction
Experimental group	1.21±0.12	1.10±0.12	1.20±0.24	0.98±0.11	0.99±0.21	0.78±0.12	0.74±0.12
Control group	2.10±0.23	2.00±0.23	2.10±0.30	1.98±0.22	1.78±0.21	1.65±0.23	1.52±0.23
t	26.574	26.873	18.146	31.492	20.605	25.977	23.290
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table 3: Comparison of quality of life scores of patients after treatment (x±s)

Groups	Mental function	Physical function	Social function	Material life state
Experimental grou	85.24±2.68	83.58±2.14	86.20±2.14	84.68±2.68
Control group	74.20±3.20	72.65±3.20	75.68±2.68	75.22±2.58
t	20.488	21.993	23.760	19.698
P	<0.001	<0.001	<0.001	<0.001

Table 4: Comparison of treatment effective rate of patients [n(%)]

Groups	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Experimental group	10(16.7)	36(60.0)	12(20.0)	2(3.3)	58(96.7)
Control group	2(3.3)	18(30.0)	24(40.0)	16(26.7)	44(73.3)
X^2	5.926	10.909	5.714	12.811	12.811
P	0.015	0.001	0.017	0.000	0.000

Moreover, the estrogen levels, β-EP levels and 5-HT levels of patients in the experimental group after treatment were significantly better than those in the control group (P<0.001), suggesting that CGLM further enhances the hormone regulation effect on the basis of Liuwei Dihuang Pills. Bupleurum and keel in the drug can regulate the function of the hypothalamic-pituitary-adrenal axis, stimulate the expression of monoamine neurotransmitters such as 5-HT and then alleviate sleep disorders and shorten sleep latency (Gong *et al.*, 2015). 5-HT is closely related to the emotional function of patients, which can reduce the negative emotions of patients such as anxiety and depression. Herein, the negative emotion score of the experimental group after treatment was significantly lower than that of the control group (P<0.001). Furthermore, the results of this study also demonstrated higher quality of life scores of patients in the experimental group than those in the control group (P<0.001). They treated patients with severe depression and insomnia with CGLM and revealed that CGLM succeeds in ameliorating the patients' quality of life. The reason is that Bupleurum yields the effect of calming the nerves, while Guizhi can tonify Yang and promote blood circulation; their combination with medicinal herbs such as Poria and Ginseng can soothe the mind and relieve the evil Qi, to finally abate the symptoms of insomnia, depression and irritability and eventually achieve a major improvement in quality of life.

CONCLUSION

CGLM combined with Liuwei Dihuang Pills can regulate the serum hormone levels of patients with menopausal insomnia, reduce negative emotions, and improve sleep quality and quality of life, which merits clinical promotion.

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