Article

J. Biol. Regul. Homeost. Agents. 2024; 38(6): 5117–5124
https://doi.org/10.23812/j.biol.regul.homeost.agents.20243806.408

Effect of Flupentixol-Melitracen in Combination with Psychotherapy on Negative Mood, Psychological Stress and Life Quality in Coronary Heart Disease Patients Complicated with Psychological Disorders

Haojie Li[1,2], Kuan Xu[1,3], Jiancong Jiang[1,3], Li Yang[1,4,*]

[1]Department of Cardiovascular Internal Medicine, Yixing Traditional Chinese Medicine Hospital, 214200 Yixing, Jiangsu, China
[2]Clinical Medical School, Jiangsu University, 212013 Zhenjiang, Jiangsu, China
[3]The First Clinical Medical College, Nanjing University of Traditional Chinese Medicine, 210029 Nanjing, Jiangsu, China
[4]Medical College, Yangzhou University, 225009 Yangzhou, Jiangsu, China
*Correspondence: yangli_lly@163.com (Li Yang)
Submitted: 29 January 2024 Revised: 1 March 2024 Accepted: 11 March 2024 Published: 1 June 2024

Background: Coronary heart disease (CHD) is a common cardiovascular disease in clinical settings, which often combines with psychological disorders. Therefore, this study aimed to investigate the impact of flupentixol-melitracen in combination with psychotherapy on CHD patients complicated with psychological disorders.

Methods: A total of 120 CHD patients with psychological disorders were divided into two groups: the control group (n = 60) and the observation group (n = 60). The patients in the former group received flupentixol-melitracen based on conventional therapy, while the latter group was additionally treated with psychotherapy on the basis of the control group. Moreover, before and after treatment, the depression and anxiety levels in patients were evaluated utilizing the scores of the Beck Depression Inventory (BDI), the Spielberg State-Trait Anxiety Inventory form 1 (STAI-state), and Spielberg State-Trait Anxiety Inventory form 2 (STAI-trait). Furthermore, the quality-of-life scoring was assessed using the questionnaire, and serum factor levels were determined by commercial kits.

Results: Compared to the levels before treatment, the BDI, STAI-state, and STAI-trait scores, hypersensitive C-reactive protein (hs-CRP), lipopolysaccharide (LPS), tumor necrosis factor alpha (TNF-α), nuclear factor-kappa B (NF-κB), and substance P (SP) were significantly decreased in both groups after treatment ($p < 0.05$). However, their levels were substantially alleviated in the observation group compared to the control group ($p < 0.01$). Furthermore, the interleukin-10 (IL-10) and 5-hydroxytryptamine (5-HT) levels were higher in the observation group compared to the control group ($p < 0.001$). After treatment, there were no abnormalities in blood pressure, blood and urine routine, and hepatorenal function in the two groups.

Conclusion: Flupentixol-melitracen in combination with psychotherapy can relieve depression and anxiety in CHD patients with psychological disorders. Furthermore, this method can improve the inflammatory level and quality of life of patients.

Keywords: flupentixol-melitracen; psychotherapy; coronary heart disease; psychological disorder; psychological stress

Introduction

Coronary heart disease (CHD) is a common clinical cardiovascular condition [1] primarily characterized by angina pectoris, arrhythmia, precordial discomfort, and others. Furthermore, approximately 69%–70.4% of CHD patients experience concomitant depressive symptoms, possibly related to the long course and recurrent nature of the disease [2]. Recent studies have shown that CHD patients exhibiting depressive symptoms face a significantly higher risk of fatal CHD events and sudden death [3,4]. Currently, flupentixol-melitracen is widely used in treating patients with mental disorders [5]. Flupenthixol-melitracen not only promotes dopamine secretion in the nerve center but also effectively regulates sympathetic nerve activity, thereby helping in treating anxiety and depression [6]. However, long-term use of this drug may lead to drug tolerance in patients [6]. Hence, it becomes necessary to investigate safer and more effective treatment approaches to further improve the therapeutic efficacy of flupentixol-melitracen for CHD patients by additional treatment methods.

Ning Zeng *et al.* [7] showed that psychotherapy effectively reduces depression and anxiety in patients with post-stroke depression, consequently improving their quality of life. Hence, it may be beneficial to extend this intervention to CHD patients with psychological disorders. At present, there are few related studies on psychotherapy combined with flupentixol-melitracen in the treatment of CHD complicated with psychological disorders. Therefore, this retrospective study aims to explore the clinical efficacy

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

of combining psychotherapy with flupentixol-melitracen in the treatment of psychological disorders in CHD patients.

Materials and Methods

Study Subjects

A total of 120 CHD patients complicated with psychological disorders, admitted to Yixing Traditional Chinese Medicine Hospital, China from June 2021 to May 2023, were enrolled in this study. Based on different treatment protocols, study subjects were divided into control (n = 60) and observation (n = 60) groups. This study was approved by the ethics committee of Yixing Traditional Chinese Medicine Hospital, China (approval number: 20210515) and adhered to the Declaration of Helsinki. Furthermore, all participants provided written informed consent.

Sample Size

The sample size was calculated following a previously described method [8]. The Generalized Anxiety Disorder Scale (GAD-7) was used to observe the anxiety level in the patients. It was assumed that after 4 weeks of treatment, patients receiving psychotherapy would have a GAD-7 score of 9.48 ± 3.47, whereas those not receiving psychotherapy would exhibit a score of 12.60 ± 3.75. The sample size was determined by PASS software (version 15.0, NCSS, Kaysville, UT, USA), assuming an efficacy of 0.9, a type 1 error of 0.05, a sample size ratio of 1:1 between two groups, and a sample dropout rate of 25%. Consequently, it was observed that the minimum sample size of each group was 40, with a total of 80 samples. After calculating the sample size, 60 samples were chosen for each group utilizing a random table method.

Diagnostic Criteria

Patients who met the diagnostic criteria for CHD as described in *Stable Coronary Artery Disease: Treatment* [9], as well as those satisfying the diagnostic criteria for mental disorders as outlined in *The Diagnostic and Statistical Manual of Mental Disorders* [10], were enrolled in this study. The diagnosis of patients was performed by a cardiovascular physician at the Yixing Traditional Chinese Medicine Hospital, China.

Inclusion Criteria

The inclusion criteria for the patients were as follows: patients who met the diagnostic criteria of western medicine, those with stable vital signs, and patients with complete clinical information, complying with the medication regulations.

Exclusion Criteria

The patients with allergic responses to flupentixol-melitracen, patients who experienced myocardial infarction within 6 months, those with severe liver, kidney, and blood diseases, and patients with autoimmune diseases were excluded from the study.

Treatment

Patients in both groups were given conventional treatment after admission, including CHD secondary prevention measures. Nitroglycerin was administered sublingually for angina pectoris. The patients in the control group were orally given flupentixol-melitracen (approval number of National Medical Products Administration: HJ20171104; manufacturer: H. Lundbeck A/S, Copenhagen, Denmark). One tablet was taken in the morning and at midday for the first five days. After this, patients took one tablet of flupentixol-melitracen every morning. Routine nursing measures were implemented, which included obtaining the patient's hospitalization information and understanding personal situations. Furthermore, we implemented measures for the prevention of infection such as urging CHD patients to avoid densely crowded places or poorly ventilated areas to reduce the risk of respiratory or digestive tract infection. Moreover, the patients were provided with dietary care guidelines, advising them to eat a low-salt, low-fat, and bland diet, avoiding consumption of animal viscera, foods with high fat, as well as fried, chilled, and spicy foods. Additionally, they were advised to avoid strenuous or stressful exercise or physical activities. Moreover, patients were suggested to visit the hospital regularly and cautioned against discontinuing medicines or self-adjusting dosage without consultation with the physician. They were counseled to quit smoking, reduce alcohol intake, and ensure enough sleep.

In the observation group, psychotherapy was combined with the treatment protocol already established in the control group. Initially, the communication between nurses and patients was enhanced to establish a good nurse-patient relationship. Secondly, a targeted intervention plan was formulated. Particularly, a research group headed by the head nurse was established to assist the intervention process. The framework and content of the intervention were developed under the guidance of the cardiology experts in our research group. Meanwhile, each session covered different topics. During the first meeting, our research team underwent a detailed discussion on the importance of psychological factors in cardiovascular health education, and the patients were introduced to the concept of mental health as well as instructed on self-monitoring methods for maintaining overall health. In the second session, the research team encouraged patients to participate in activities that lead to overall well-being. During the third meeting, the research team encouraged patients to identify thoughts and

beliefs that may negatively affect their mental health and subsequently focused on analyzing patients' inner distress and contradictions to facilitate psychological counseling on patients. The subsequent meeting from 4th-6th primarily investigated various aspects of the patient's living environment, personal growth, life goals, self-acceptance, positive relationship, and so on. During this period, emphasis was placed on identifying specific deficits that participants might experience in each of these dimensions and actively struggling to improve them. Furthermore, during the 7th–8th meetings, patients were engaged in exercise sessions, during which the research team asked participants to assess their mental health before and after the activities. Additionally, they were instructed on how to integrate these skills into their daily lives. The treatment course for both groups was 4 weeks, following protocols from previous studies with minor modifications [8,11].

Observation Indicators

The observational indicators evaluated during the study were as follows:

Evaluating depression and anxiety: Before and after treatment, the depression and anxiety levels of patients within the two groups were evaluated employing the Beck Depression Inventory (BDI) scores, Spielberg State-Trait Anxiety Inventory form 1 (STAI-state), and Spielberg State-Trait Anxiety Inventory form 2 (STAI-trait). The BDI scale included 21 items [12], and each item was scored on a scale of 0 to 3 levels, yielding a total score range of 0 to 63 points. The higher score indicated more severity of depression in the patient. The anxiety of patients in the two groups was measured by STAI. The STAI scale contained two units, each containing 20 questions. The first section measured state anxiety (reflecting the immediate feelings of the patient when completing the questionnaire), and the second section assessed trait (habitual) anxiety. The higher scores indicated greater levels of anxiety in the patient [13].

Quality of life scoring [14]: The questionnaire included 27 questions in the physical, social, and emotional domains. Responses were rated on a 7-point scale, with higher scores implying better quality of life.

Assessing serum factor levels: Before and after treatment, 5 ml of venous blood samples were collected from all patients, and then the serum was separated through centrifugation and stored at –20 °C. The expression levels of serum nuclear factor-kappa B (NF-κB, 650.090.096, Kerui Mei Technology Co., Ltd., Beijing, China), hypersensitive C-reactive protein (hs-CRP, 850.700.X, Kerui Mei Technology Co., Ltd., Beijing, China), tumor necrosis factor alpha (TNF-α, 950.090.X, Kerui Mei Technology Co., Ltd., Beijing, China), and interleukin-10 (IL-10, 950.060.X, Kerui Mei Technology Co., Ltd., Beijing, China) were determined using enzyme-linked immunosorbent assay (ELISA) kits. Furthermore, serum lipopolysaccharide (LPS) levels were assessed employing a Limulus reagent dynamic turbidimetric test with kits purchased from Haling Biotechnology Co., Ltd. (HLE11057, Shanghai, China). These above procedures were performed following the instructions provided with the respective kits, and the experimental results were recorded.

Observing the safety: During the treatment period, patients were assisted to perform weekly assessments such as blood pressure, blood and urine routine, and liver and kidney function tests. These assessments were performed by a cardiovascular physician using a blind method.

Statistical Methods

SPSS 20.0 (Applied Biosystems, Foster City, CA, USA) was employed for statistical analyses. Enumeration data were compared using the χ^2-test. Meanwhile, measurement data were presented as the mean ± standard deviation. Moreover, the independent sample *t*-test was used for comparison between the two groups, and one-way analysis of variance (ANOVA) was adopted for comparison at different time points in the same group, followed by the post-hoc analysis of the Bonferroni test. Additionally, the Kolmogorov-Smirnov method was used for evaluating normality in the data. A p-value < 0.05 was considered statistically significant.

Results

Comparison of Depression, Anxiety, and Quality of Life Scales before and after Treatment between the Two Groups

The baseline characteristics of patients in both the control and observation groups are shown in Table 1, which are not significantly different ($p > 0.05$) and comparable. From admission to the 4-week rehabilitation plan until discharge, the BDI score in the control group changed from 20.00 ± 1.76 points to 17.82 ± 1.58 points (Table 2, $p < 0.05$), the STAI-state score reduced from 32.07 ± 2.84 points to 26.72 ± 2.19 points (Table 2, $p < 0.05$), the STAI-trait score decreased from 36.98 ± 2.73 points to 26.10 ± 2.13 points (Table 2, $p < 0.05$), and the quality of life score increased from 120.02 ± 10.99 points to 139.28 ± 12.40 points (Table 2, $p < 0.05$). In the observation group, the BDI score decreased from 20.37 ± 1.73 points to 13.18 ± 1.30 points (Table 2, $p < 0.05$), the STAI-state score reduced from 33.08 ± 2.99 points to 16.78 ± 1.64 points (Table 2, $p < 0.05$), the STAI-trait score declined from 36.88 ± 3.07 points to 18.97 ± 1.79 points (Table 2, $p < 0.05$), and quality of life score increased from 122.13 ± 11.59 points to 146.12 ± 13.21 points (Table 2, $p < 0.05$). Additionally, the scores of BDI, STAI-state, and STAI-trait in the observation group were significantly lower compared to the control group (Table 2, $p < 0.05$), while the quality of life score in the observation group was substantially higher than in the control group (Table 2, $p < 0.05$). Collectively, both groups of patients showed improvement in depression, anxiety, and

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Table 1. Baseline clinical characteristics of study participants.

Variable	Control (n = 60)	Observation (n = 60)	t/χ^2	p
Sex (male) [n (%)]	39 (65.00)	36 (60.00)	0.320	0.572
Age (years)	61.25 ± 11.17	62.08 ± 10.91	0.413	0.680
Height (cm)	164.74 ± 7.44	163.96 ± 7.25	0.579	0.564
Weight (kg)	62.23 ± 11.37	62.31 ± 9.75	0.041	0.967
Smoking [n (%)]	13 (21.67)	15 (25.00)	0.186	0.666
Alcohol [n (%)]	1 (1.67)	3 (5.00)	1.034	0.309
Systolic BP (mmHg)	133.12 ± 19.06	134.30 ± 15.20	0.376	0.708
Diastolic BP (mmHg)	75.03 ± 14.01	73.28 ± 15.89	0.640	0.523
Hypertension [n (%)]	37 (61.67)	34 (56.67)	0.310	0.577
Heart failure [n (%)]	4 (6.67)	3 (5.00)	0.152	0.697
Diabetes mellitus [n (%)]	8 (13.33)	6 (10.00)	0.323	0.570
Hyperlipemia [n (%)]	14 (23.33)	12 (20.00)	0.196	0.658
ACEI/ARB [n (%)]	21 (35.00)	18 (30.00)	0.342	0.559
β-blocker [n (%)]	31(51.67)	25 (41.67)	1.205	0.272
CCB [n (%)]	14 (23.33)	16 (26.67)	0.178	0.673
Hemoglobin (g/L)	135.31 ± 26.71	135.43 ± 22.03	0.027	0.979
Blood glucose (mmol/L)	8.34 ± 3.95	7.75 ± 3.95	0.823	0.412
Cholesterol (mmol/L)	4.92 ± 1.46	4.75 ± 1.03	0.735	0.464
HDL-C (mmol/L)	1.44 ± 0.67	1.28 ± 0.34	1.671	0.097
LDL-C (mmol/L)	3.04 ± 0.94	3.11 ± 1.06	0.385	0.701
TG (mmol/L)	1.89 ± 0.80	1.69 ± 0.63	1.503	0.136

Abbreviation: BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Table 2. Comparison of depression, anxiety, and quality of life scales before and after treatment between the two groups.

Group	n	BDI (Score)		STAI-state (Score)		STAI-trait (Score)		Quality of life (Score)	
		Before	After	Before	After	Before	After	Before	After
Control	60	20.00 ± 1.76	17.82 ± 1.58*	32.07 ± 2.84	26.72 ± 2.19*	36.98 ± 2.73	26.10 ± 2.13*	120.02 ± 10.99	139.28 ± 12.40*
Observation	60	20.37 ± 1.73	13.18 ± 1.30*	33.08 ± 2.99	16.78 ± 1.64*	36.88 ± 3.07	18.97 ± 1.79*	122.13 ± 11.59	146.12 ± 13.21*
t		1.153	17.580	1.911	28.160	0.188	19.850	1.026	2.922
p		0.251	<0.001	0.059	<0.001	0.851	<0.001	0.307	0.004

*Before vs after, $p < 0.05$. Abbreviation: BDI, Beck Depression Inventory; STAI-state, Spielberg State-Trait Anxiety Inventory form 1; STAI-trait, Spielberg State-Trait Anxiety Inventory form 2.

Table 3A. Comparison of serum factor levels before and after treatment between the two groups.

Group	n	hs-CRP (mg/L)		LPS (EU/L)		TNF-α (ng/L)		NF-κB (μg/L)	
		Before	After	Before	After	Before	After	Before	After
Control	60	29.24 ± 4.85	21.25 ± 2.45*	24.12 ± 2.25	18.21 ± 1.56*	52.17 ± 7.05	37.92 ± 4.91*	11.84 ± 2.16	8.76 ± 1.56*
Observation	60	28.98 ± 4.94	15.47 ± 1.33*	24.89 ± 2.42	11.34 ± 1.23*	51.94 ± 6.88	28.43 ± 2.10*	11.94 ± 2.17	6.18 ± 1.04*
t		0.291	16.070	1.803	26.791	0.181	13.770	0.255	10.660
p		0.772	<0.001	0.074	<0.001	0.857	<0.001	0.800	<0.001

*Before vs after, $p < 0.05$. Abbreviation: hs-CRP, hypersensitive C-reactive protein; LPS, lipopolysaccharide; NF-κB, nuclear factor-kappa B; TNF-α, tumor necrosis factor alpha.

quality of life after treatment. Additionally, the improvement impacts observed in the observation group were more significant compared to the control group.

Comparison of Serum Factor Levels before and after Treatment between the Two Groups

Compared to the levels before the 4-week treatment, the levels of hs-CRP (from 29.24 ± 4.85 mg/L to 21.25 ± 2.45 mg/L), LPS (from 24.12 ± 2.25 EU/L to 18.21 ± 1.56 EU/L), TNF-α (from 52.17 ± 7.05 ng/L to 37.92 ±

Table 3B. Comparison of serum factor levels before and after treatment between the two groups.

Group	n	SP (ng/mL)		IL-10 (ng/L)		5-HT (μg/L)	
		Before	After	Before	After	Before	After
Control	60	106.36 ± 17.24	87.16 ± 10.39*	87.64 ± 8.44	98.98 ± 10.12*	82.95 ± 9.62	99.34 ± 13.36*
Observation	60	105.85 ± 17.21	66.45 ± 6.02*	88.12 ± 8.70	115.54 ± 11.54*	83.34 ± 19.47	107.67 ± 13.09*
t		0.163	13.360	0.307	8.356	0.139	3.450
p		0.871	<0.001	0.759	<0.001	0.890	0.001

*Before vs after, $p < 0.05$. Abbreviation: SP, substance P; IL-10, interleukin-10; 5-HT, 5-hydroxytryptamine.

Table 4. The incidence of adverse reactions was compared between the two groups.

Group	n	Blood pressure	Blood and urine routine	Hepatorenal function
Control	60	0	0	0
Observation	60	0	0	0

4.91 ng/L), NF-κB (from 11.84 ± 2.16 μg/L to 8.76 ± 1.56 μg/L), and substance P (SP, from 106.36 ± 17.24 ng/mL to 87.16 ± 10.39 ng/mL) in the control group were significantly alleviated after the treatment (Table 3A and 3B, $p < 0.001$), while the levels of IL-10 (from 87.64 ± 8.44 ng/L to 98.98 ± 10.12 ng/L) and 5-hydroxytryptamine (5-HT, from 82.95 ± 9.62 μg/L to 99.34 ± 13.36 μg/L) were elevated after the treatment (Table 3B, $p < 0.001$). Similarly, the observation group showed a substantial decrease in the levels of hs-CRP (from 28.98 ± 4.94 mg/L to 15.47 ± 1.33 mg/L), LPS (from 24.89 ± 2.42 EU/L to 11.34 ± 1.23 EU/L), TNF-α (from 51.94 ± 6.88 ng/L to 28.43 ± 2.10 ng/L), NF-κB (from 11.94 ± 2.17 μg/L to 6.18 ± 1.04 μg/L), and SP (from 105.85 ± 17.21 ng/mL to 66.45 ± 6.02 ng/mL), but a significant increase in the levels of IL-10 (from 88.12 ± 8.70 ng/L to 115.54 ± 11.54 ng/L) and 5-HT (from 83.34 ± 19.47 μg/L to 107.67 ± 13.09 μg/L) was observed following the 4-week treatment (Table 3A and 3B, $p < 0.001$). Furthermore, the levels of hs-CRP, LPS, TNF-α, NF-κB, and SP were significantly reduced in the observation group compared to the control group (Table 3A and 3B, $p < 0.05$), while IL-10 and 5-HT levels were substantially higher in the observation group (Table 3B, $p < 0.05$). In conclusion, a significant reduction was observed in the inflammation level in both groups after treatment, with the observation group exhibiting a lower inflammation level compared to the control group.

Adverse Reactions

Following treatment, there were no abnormalities in blood pressure, blood and urine routine, and hepatorenal function in the two groups (Table 4), indicating the safety of the treatment.

Discussion

In recent years, the incidence of CHD has increased annually [1]. Certain CHD patients experience anxiety, depression, and other psychological disorders. Long-term anxiety and depression stimulate sympathetic excitation of the nervous system, enhancing myocardial contraction and accelerating heart rate, which in turn aggravates angina pectoris in patients [15]. Furthermore, sympathetic excitation of the nervous system affects glycolipid metabolism, causing atherosclerosis, further accelerating the progression of CHD and significantly affecting the overall health of patients [15]. Therefore, how to find an effective way to treat CHD patients with psychological disorders has attracted much attention from clinical health care workers.

Flupentixol-melitracen is a compound preparation primarily composed of flupentixol and melitracen [16]. Flupentixol serves as a nerve blocker, increasing the synthesis and release of dopamine in the synaptic cleft by blocking the D2 receptor of dopamine, thereby contributing to its anti-anxiety and anti-depression effects [17]. The melitracen, a biphasic antidepressant, exerts an antidepressant effect by inhibiting the reuptake of serotonin and norepinephrine in the presynaptic membrane, resulting in a significant increase in the neurotransmitter levels in the synaptic cleft, thereby enhancing synaptic transmission [18]. Su *et al.* [8] found that administering flupentixol-melitracen can improve the clinical efficacy, reduce myocardial load and injury, ameliorate cardiac function, and effectively reduce the depression of patients with CHD complicated by heart failure and depression. Furthermore, it has been underscored that psychological intervention in combination with flupentixol and melitracen tablets can remarkably decrease the level of anxiety in patients with CHD complicated with anxiety disorder [19]. Psychotherapy mainly aims to identify the causes of patients' psychological disorders from the root by formulating targeted intervention plans, so as to eliminate the patients' internal concerns, assist patients in adjusting their psychological status and further stabilize the treatment effect [20]. Nikrahan *et al.* [21] indicated the feasibility of improving the clinical psychological outcomes of CHD patients. Importantly, psychotherapy in combination with flupentixol-melitracen proves effective in treating CHD patients with psychological disorders, which can ameliorate patients' anxiety and depression, and improve

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

compliance with doctors [8]. The outcomes of this study showed that after treatment, the scores of BDI, STAI-state, and STAI-trait in the two groups were significantly reduced than those before treatment, and the quality-of-life score was obviously increased after the treatment. Furthermore, the scores of BDI, STAI-state, and STAI-trait in the observation group were significantly alleviated compared to the control group, while the quality-of-life score was higher than that in the control group. These results indicated the significant efficacy of flupentixol-melitracen in combination with psychotherapy in CHD patients complicated with psychological disorders. The combined intervention can not only reduce depression and anxiety but also improve the life quality of patients.

The pathologic basis of CHD originates from atherosclerosis, where inflammation plays an important role in plaque rupture, thrombosis, and vascular endothelial injury [22]. Myocardial ischemia induces the body's defense system, leading to the secretion of inflammatory factors such as hs-CRP, LPS, and TNF-α. This disrupts the balance between inflammation and anti-infection in CHD patients, thus affecting the nervous function of the prefrontal cortex-limbic system and significantly increasing the risk of concurrent mental disorders [23]. Admittedly, the roles of inflammatory factors in CHD have been confirmed in many studies, underscoring their role in psychological disorders. Particularly, TNF-α is identified as an essential factor involved in plaque formation and endothelial dysfunction during the process of CHD [24]. Within the central nervous system, TNF-α can inhibit hippocampal neurogenesis and promote the expression of indoleamine 2,3-dioxygenase in both central and peripheral immunoreactive cells, thus affecting the hippocampal neurons and 5-HT metabolism, ultimately contributing to depressive symptoms [25]. Additionally, TNF-α can cause neuronal death or induce apoptosis, resulting in anxiety and depression disorders [26,27]. Extensive research evidence has shown that hs-CRP is one of the independent risk factors for CHD in individuals with anxiety disorders [28]. Inhibition of the NF-κB pathway can contribute to the alleviation of endothelial cell inflammatory injury in CHD [29]. Furthermore, IL-10 is an anti-inflammatory cytokine predominantly produced by macrophages and Th2 lymphocytes and possesses a variety of anti-atherosclerotic properties, including inhibition of macrophages and monocyte endothelial infiltration as well as NF-κB activation [30]. Additionally, LPS can lead to endothelium dysfunction, which represents one of the risk factors associated with CHD [31].

This study showed that after treatment, the levels of hs-CRP, LPS, TNF-α, NF-κB, and SP were decreased in the two groups, while the levels of IL-10 and 5-HT were increased. Additionally, compared to the control group, the levels of hs-CRP, LPS, TNF-α, NF-κB, and SP were significantly reduced in the observation group, whereas the levels of IL-10 and 5-HT were elevated. These findings suggest that flupentixol-melitracen in combination with psychotherapy regulates the inflammatory levels of CHD patients with psychological disorders. It has been indicated that flupentixol-melitracen can exert an inhibitory effect on the hyperactivity of the HPA axis, and inhibit the synthesis and secretion of inflammatory factors by regulating the release of Cor, thereby maintaining the body's homeostasis [16,32]. Exercise, cited in psychotherapy, can alleviate the rate of skeletal muscle degeneration, enhance muscle strength, and reduce visceral fat mass and adipokine release, thereby improving the body's inflammatory environment [20]. Yang *et al*. [33] proved that properly executed quantitative functional exercise effectively alleviated the inflammatory response and improved the rehabilitation ability of patients with hip fractures.

In this study, both the experimental groups exhibited no abnormalities in blood pressure, blood and urine routine, and hepatorenal function following treatment, implying that the combination of flupentixol-melitracen and psychotherapy is safe for CHD patients with psychological disorders. This is because the two components contained in flupentixol-melitracen not only synergistically regulate the central nervous system but also counteract the extrapyramidal symptoms induced by flupentixol, which is often manifested as the synergistic effect of treatment and the antagonistic effect of side effects [34,35]. Heng *et al*. [36] found that the clinical adverse reactions associated with flupentixol-melitracen were less and mild. Nevertheless, it should be acknowledged that we cannot fully guarantee that patients can maintain psychological balance without medication. Therefore, we did not establish a separate psychotherapy group to minimize potential interference with patients' normal treatment.

Conclusion

In summary, the combination of flupentixol-melitracen and psychotherapy has excellent effect on CHD patients with psychological disorders, effectively reducing depression and anxiety. Furthermore, it has high safety and can improve the inflammatory level and life quality of patients.

Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Author Contributions

Substantial contributions to conception and design: HJL. Data acquisition, data analysis and interpretation: KX, JCJ, LY. Drafting the article or critically revising it for important intellectual content: All authors. Final approval of

the version to be published: All authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved: All authors.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Yixing Traditional Chinese Medicine Hospital, China (approval number: 20210515) and adhered to the Declaration of Helsinki. Furthermore, all participants provided written informed consent.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Wirtz PH, von Känel R. Psychological Stress, Inflammation, and Coronary Heart Disease. Current Cardiology Reports. 2017; 19: 111.

[2] Nezafati MH, Vojdanparast M, Nezafati P. Antidepressants and cardiovascular adverse events: A narrative review. ARYA Atherosclerosis. 2015; 11: 295–304.

[3] Moludi J, Khedmatgozar H, Nachvak SM, Abdollahzad H, Moradinazar M, Sadeghpour Tabaei A. The effects of co-administration of probiotics and prebiotics on chronic inflammation, and depression symptoms in patients with coronary artery diseases: a randomized clinical trial. Nutritional Neuroscience. 2022; 25: 1659–1668.

[4] Wang Y, Wang Y. Analysis of the development course of traditional Chinese medicine standardization and recommendations on future work. Guidelines and Standards of Chinese Medicine. 2023; 1: 1–8. (In Chinese)

[5] Zhang Y, Becker T, Kösters M. Preliminary study of patterns of medication use for depression treatment in China. Asia-Pacific Psychiatry. 2013; 5: 231–236.

[6] Hu L, Shen L, Li D, Huang M, Xiao X, Chen S. The combination therapy with esomeprazole and flupenthixol/melitracen in symptom improvement of erosive gastritis complicated with negative feelings compared with Esomeprazole alone. Cellular and Molecular Biology. 2020; 66: 15–19.

[7] Zeng N, Chen KH, Zheng HL, Liu ZY. Application of structural group psychotherapy combined with social interaction training in patients with post-stroke depression. China Medical Herald. 2022; 19: 171–174. (In Chinese)

[8] Su CY, Shuai DD, Wang L, Zhao X. Psychotherapy Combined with Flupentixol-melitracen on the Clinical Efficacy and Negative Emotion of Patients with Coronary Heart Disease Complicated by Psychological Disorders. Journal of Medical Information. 2021; 34: 155–157. (In Chinese)

[9] Braun MM, Stevens WA, Barstow CH. Stable Coronary Artery Disease: Treatment. American Family Physician. 2018; 97: 376–384.

[10] Battle DE. Diagnostic and Statistical Manual of Mental Disorders (DSM). CoDAS. 2013; 25: 191–192.

[11] He ZM, Li YH, Kang YP, Ren YL, Wang RR, Liu WX. Effect of Flupentixol Melitracen Combined with Psychological Intervention on Cardiac Function, Psychological State and Quality of Life in Patients with Chronic Heart Failure Complicated with Depression and Anxiety. Progress in Modern Biomedicine. 2021; 21: 2848–2852. (In Chinese)

[12] Daws RE, Timmermann C, Giribaldi B, Sexton JD, Wall MB, Erritzoe D, *et al*. Increased global integration in the brain after psilocybin therapy for depression. Nature Medicine. 2022; 28: 844–851.

[13] Becklund AL, Rapp-McCall L, Nudo J. Using weighted blankets in an inpatient mental health hospital to decrease anxiety. Journal of Integrative Medicine. 2021; 19: 129–134.

[14] Naderi N, Bakhshandeh H, Amin A, Taghavi S, Dadashi M, Maleki M. Development and Validation of the First Iranian Questionnaire to Assess Quality of Life in Patients With Heart Failure: IHF-QoL. Research in Cardiovascular Medicine. 2012; 1: 10–16.

[15] Blumenthal JA, Smith PJ, Jiang W, Hinderliter A, Watkins LL, Hoffman BM, *et al*. Effect of Exercise, Escitalopram, or Placebo on Anxiety in Patients With Coronary Heart Disease: The Understanding the Benefits of Exercise and Escitalopram in Anxious Patients With Coronary Heart Disease (UNWIND) Randomized Clinical Trial. JAMA Psychiatry. 2021; 78: 1270–1278.

[16] Zheng Y, Jia C, Jiang X, Chen J, Chen XL, Ying X, *et al*. Electroacupuncture effects on the P2X4R pathway in microglia regulating the excitability of neurons in the substantia gelatinosa region of rats with spinal nerve ligation. Molecular Medicine Reports. 2021; 23: 175.

[17] Flupentixol. Nursing Times. 2006; 102: 31.

[18] Wang X, Xiong J, Yang J, Yuan T, Jiang Y, Zhou X, *et al*. Meta-analysis of the clinical effectiveness of combined acupuncture and Western Medicine to treat post-stroke depression. Journal of Traditional Chinese Medicine. 2021; 41: 6–16.

[19] Liu R. Clinical effect of psychological intervention combined with Flupentixol and Melitracen Tablets in the treatment of coronary geart disease complicated with anxiety disorder. China Modern Medicine. 2020; 27: 40–42,46. (In Chinese)

[20] Gilbert P. Psychotherapy for the 21st century: An integrative, evolutionary, contextual, biopsychosocial approach. Psychology and Psychotherapy. 2019; 92: 164–189.

[21] Nikrahan GR, Eshaghi L, Massey CN, Hemmat A, Amonoo HL, Healy B, *et al*. Randomized controlled trial of a well-being intervention in cardiac patients. General Hospital Psychiatry. 2019; 61: 116–124.

[22] Toutouzas K, Benetos G, Drakopoulou M, Deligianni C, Spengos K, Stefanadis C, *et al*. Incremental predictive value of carotid inflammation in acute ischemic stroke. Stroke. 2015; 46: 272–274.

[23] Fioranelli M, Bottaccioli AG, Bottaccioli F, Bianchi M, Rovesti M, Roccia MG. Stress and Inflammation in Coronary Artery Disease: A Review Psychoneuroendocrineimmunology-Based. Frontiers in Immunology. 2018; 9: 2031.

[24] Han QQ. Tumour necrosis factor in relation to coronary heart disease and coronary artery bypass grafting. Acta Universitatis Medicinalis Anhui. 2010; 31: 1689–1690. (In Chinese)

[25] Luzina IG, Todd NW, Sundararajan S, Atamas SP. The cytokines of pulmonary fibrosis: Much learned, much more to learn. Cytokine. 2015; 74: 88–100.

[26] Bagdonas E, Raudoniute J, Bruzauskaite I, Aldonyte R. Novel aspects of pathogenesis and regeneration mechanisms in COPD. International Journal of Chronic Obstructive Pulmonary Disease. 2015; 10: 995–1013.

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

[27] Sasayama D, Hattori K, Wakabayashi C, Teraishi T, Hori H, Ota M, *et al*. Increased cerebrospinal fluid interleukin-6 levels in patients with schizophrenia and those with major depressive disorder. Journal of Psychiatric Research. 2013; 47: 401–406.

[28] Bankier B, Barajas J, Martinez-Rumayor A, Januzzi JL. Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. European Heart Journal. 2008; 29: 2212–2217.

[29] Kuszynski DS, Lauver DA. Pleiotropic effects of clopidogrel. Purinergic Signalling. 2022; 18: 253–265.

[30] Yang MY, Li KR, He HY. Relationship between IL-10 and related pro-inflammatory factors and the extent of coronary artery disease in patients with coronary heart disease and metabolic syndrome. Guangdong Medical Journal. 2021; 42: 988–991. (In Chinese)

[31] Li L, He M, Zhou L, Miao X, Wu F, Huang S, *et al*. A solute carrier family 22 member 3 variant rs3088442 G→A associated with coronary heart disease inhibits lipopolysaccharide-induced inflammatory response. The Journal of Biological Chemistry. 2015; 290: 5328–5340.

[32] Zhang T, Yu GD. Observation of Flupentixol and melitracen on curative effect of sudden deafness patients with anxiety and depression in different stages. Journal of Clinical Otorhinolaryngology, Head, and Neck Surgery. 2018; 32: 643–646. (In Chinese)

[33] Yang J, Li Q, Chang CF. Effect of Early Quantitative Functional Exercise on Blood Rheology and Inflammatory Factors in Patients with Hip Fracture. Chinese Journal of Thrombosis and Hemostasis. 2020; 26: 250–251,254. (In Chinese)

[34] Ruan Z, Wan Z, Yang L, Li W, Wang Q. JAK/STAT signalling regulates antimicrobial activities in Eriocheir sinensis. Fish & Shellfish Immunology. 2019; 84: 491–501.

[35] Luo X, Wang L, Fang S, Qing X, Jiang T, Yang Y, *et al*. Chinese Herbal Medicine for Functional Dyspepsia With Psychological Disorders: A Systematic Review and Meta-Analysis. Frontiers in Neuroscience. 2022; 16: 933290.

[36] Heng QX, Zhang H. Effect of Psycho-Cardiology Medical Mode in Coronary Heart Disease Patients with Anxiety and Depression in Primary Hospital. Heman Medical Research. 2022; 31. (In Chinese)