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Research Article

Clinical Study of Psycho-cardiology Combined with FNS in the Treatment of SCAD with Depression

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Abstract

To investigate the effects of psycho-cardiology combined with fastigial nucleus stimulation (FNS) on patients with stable coronary artery disease (SCAD) complicated with depression, we observed the changes of concentrations of N-terminal pro-B type natriuretic peptide (NT-proBNP), tumor necrosis factor-α(TNF-α), 5-hydroxytryptamine (5-HT), dopamine (DA) and depressive symptoms in these patients. One hundred and fifty patients, who were hospitalized the Department of Cardiology at the Third People's Hospital of Mianyang from February 2020 to October 2021 with a confirmed diagnosis of SCAD combined with depression, were selected as study subjects. Patients were randomly divided into a control group, a psycho-cardiology treatment group and a combined treatment group. The control group was given conventional treatment of SCAD and pseudo-stimulation of the fastigial nucleus, the psycho-cardiology treatment group was given conventional treatment of SCAD, psychological interventions and pseudo-stimulation of the fastigial nucleus, and the combined treatment group was given conventional treatment of SCAD, psychological intervention and FNS. The changes of concentrations of TNF-α, NT-proBNP, 5-HT and DA were observed in the three groups of patients, and the changes of the state of depression were assessed by Hamilton Depression Scale (HAMD). Serum NT-proBNP and TNF-α concentrations decreased significantly after treatment in the three groups. Especially, the decrease in the combined treatment group was the most significant($p<0.05$). Serum 5-HT and DA concentrations were not statistically different in the three groups before and after treatment ($p>0.05$). However, they were significantly higher in the psycho-cardiology treatment group and the combined treatment group($p<0.05$) and the increase in the combined treatment group was more significant than in the psycho-cardiology treatment group. In the control group, the difference of HAMD scores was not statistically significant before and after treatment ($p>0.05$), in the psycho-cardiology treatment group and the combined treatment group, the scores decreased significantly after treatment compared to before treatment ($p<0.05$). Furthermore, compared to the psycho-cardiology treatment group, the decrease was more significant in the combined treatment group ($p<0.05$). Our data suggested that Psycho-cardiology medicine combined with FNS can effectively reduce the level of serum NT-proBNP and TNF-α, increase the serum concentrations of 5-HT and DA and improve the symptoms of depression in patients with SCAD complicated with depression.

Keywords

Psycho-cardiology Treatment, Fastigial Nucleus Stimulation, Stable Coronary Artery Disease, Depression

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1. Preface

In "China Cardiac Health and Disease report 2023", it is pointed out that the mortality rate of stable coronary heart disease (SCAD) in China is on the rise [1]. With regard to the risk factors of SCAD in addition to the well-known dyslipidemia, hypertension, diabetes and so on, depression is also one of the risk factors so that it should not be ignored. It is closely related to the occurrence, development and prognosis of SCAD and can increase the morbidity and mortality of acute coronary syndrome [2-4]. Some studies have shown that excessive activation of inflammatory factors is one of the co-disease mechanisms of SCAD and depression. However, the correlation between them decreased significantly after adjusting the concentration of inflammatory factors [9]. Through a multi-center clinical study, it was found that the incidence of depressive symptoms reached 46.6% among hospitalized patients with SCAD [5]. Therefore, comprehensive and effective treatment is needed to restrain the progress in these patients, so as to improve the quality of life and reduce the economic burden. Previous clinical studies have shown that psycho-cardiology treatment can effectively improve the prognosis of patients with SCAD complicated with depression [8]. Cerebellar fastigial nucleus is located at the top of the fourth ventricle and is the classic subcortical motor coordinator which may play a key functional role in the cerebellum [10]. Some studies have shown that fastigial nucleus stimulation (FNS) can increase vagus nerve activity [11-13], regulate neurotransmitters [14, 15], improve heart rate variability [16], inhibit inflammatory response [17, 18] and improve the prognosis of patients with SCAD. In addition, cerebellar fastigial nucleus plays a key role in cognitive affective syndrome (executive function, spatial cognitive and language disorders). It can regulate emotion through direct projections of γ-aminobutyric and glutaminergic nerves in the cerebellum and hypothalamus [19, 20]. A number of clinical studies have shown that FNS can significantly improve post-stroke depression [21, 22].

In view of the correlation between SCAD and depressive symptoms, the purpose of this study is to explore the effect of the psycho-cardiology treatment combined with FNS on patients with SCAD and depression, so as to improve the prognosis and provide a new non-drug treatment for the treatment of SCAD.

2. Research Objects and Methods

2.1. Objects

150 patients with the persistence of SCAD and depression were selected from February 2020 to October 2021 in Mianyang third people's Hospital.

2.1.1. Inclusion Criteria

A. Inclusion criteria for SCAD: patients, who were diagnosed as SCAD in accordance with the 15th edition of the diagnostic criteria of "practical internal medicine", can be classified as chronic stable exertional angina pectoris, ischemic cardiomyopathy and patients with stable course after acute coronary syndrome according to the 2020 edition of "guidelines for primary diagnosis and treatment of stable coronary heart disease". B. SCAD diagnostic criteria (Meet one of the following conditions): a. electrocardiogram examination showed typical ischemic changes in the ST-T segment or old myocardial infarction; b. the result of exercise electrocardiogram test was positive; c. coronary angiography showed that the lumen diameter of one coronary artery was reduced by at least 50%. C. The Hamilton Depression Scale (HAMD) scores of patients with depressive mood were greater than 8 and the patients were diagnosed as depressive disorder by psychiatrists. D. Patients were willing to participate in treatment and had signed informed consent forms.

2.1.2. Exclusion Criteria

A. Patients had severe chronic heart failure, severe hepatic renal insufficiency or malignant tumors. B. Patients received other antidepressants 3 months before this treatment. C. Patients did not complete the questionnaire. D. Patients were at high risk of suicide and self-harm after being evaluated by a psychiatrist.

2.2. Experimental Methods

2.2.1. Grouping and Processing of Research Objects

According to the method of random drawing, they were divided into a control group and an experimental group. The experimental group was randomly divided into two groups: psycho-cardiology treatment group and combined treatment group. The control group was given standardized drugs for SCAD (refer to the edition of "guidelines for basic diagnosis and treatment of stable coronary heart disease" published in 2020) and cerebellar fastigial nucleus pseudo-stimulation. The psycho-cardiology treatment group was given standardized drugs for SCAD, cerebellar fastigial nucleus pseudo-stimulation, and psychological intervention twice a week. [including: A. patient explanation of the disease: the physician and the nurse patiently told the patients the etiology, mechanism and current treatment plan of SCAD; B. improvement of life style: health education was given to patients according to etiology and mechanism of SCAD, such as telling patients to monitor blood pressure, blood sugar, low-salt and low-fat diet, quit smoking and alcohol, have more meals a day but less food each, rest on time, exercise properly, relax and so on; C. psychological comfort: gave the trust of the patients, explained the questions patiently raised by the patients and cooperated with the family members of the patients to encourage the patients to overcome the disease together,

paid attention to the changes of the patients' psychological state and reduced the patients' negative emotions such as guilt; D. give relaxation training, such as breathing relaxation, muscle relaxation, proper exercise and so on [6]; E. oral administration of selective serotonin reuptake inhibitor (SSRI) [7] (sertraline 50mg, oral, once a day. Zhejiang Jingxing Pharmaceutical Co., Ltd., Chinese medicine standard H20051076)]. Combined treatment group: standardized drug treatment of SCAD, psychological intervention and FNS treatment were all given.

2.2.2. Treatment and Parameter Setting of FNS

A patient lay quietly in the hospital bed. Physician wiped the posterior mastoid of both ears with sterilized cotton balls, attached the disposable electrode piece to the bilateral mastoid and connected the electrode wire of the cerebellar fastigial nucleus electrical stimulator (CVFT series of Shanghai Renhe Medical equipment Co., Ltd.). By pasting the electrodes on both sides of the mastoid process, the biomimetic electrical stimulation was introduced into the cerebellar fastigial nucleus area. Besides, the output current was not greater than 5mA, and the skull disorder could be overcome, as long as the patient had no discomfort. The instrument parameters were set to mode 3, frequency 136Hz, intensity 45% ~ 90%. Every treatment lasted 30 minutes, once a day for 2 weeks.

2.3. Statistical Methods

Statistical analysis was performed using IBM SPSS, Version 23.0. The measurement data were described by normal distribution. One-way ANOVA was used to compare the data among the three groups. LSD test was used when the variance was uniform between groups. Tamheni test was used when the variance was uneven, and paired t-test was used for intra-group comparison. When the measurement data do not conform to the normal distribution, the quartile method is used to use M (Q1 and Q3), and the Kruskal-Wallis test is used to compare the three groups of data. The counting data were described by percentage (%) and the chi-square test was used. The test level is bilateral $\alpha = 0.05$. $P < 0.05$ was considered. statistically significant

3. Results

3.1. Effect of FNS Combined with Psycho-Cardiology Treatment on NT-proBNP in Patients with SCAD and Depression

The concentrations of serum N-terminal pro-B type natriuretic peptide (NT-proBNP) in the three groups were analyzed before and after treatment. Intra group comparison: The results showed that there were significant differences among the control group, the psycho-cardiology treatment group and the combined treatment group before and after treatment ($p< 0.05$). Inter group comparison: Before treatment, there was no significant difference among the control group, the psycho-cardiology treatment group and the combined treatment group ($p>0.05$). After treatment, the concentration of serum NT-proBNP in the combined treatment group was significantly lower than that in the control group and psycho-cardiology treatment group ($p < 0.05$). See Table 1.

Table 1. *Comparison of NT-proBNP in three groups before and after treatment and between groups (pg/ml).*

Variable	Control group(n=50)	psycho-cardiology treatment group(n=50)	Combined treatment group(n=50)	F/T	P
NT-proBNPBefore treatment	412.9 ±36.1	406.6 ±42.1	418.5 ±34.9	1.249	0.290
NT-proBNPAfter treatment	367.3 ±17.0☆	334.6 ±14.4☆	292.7 ±21.1☆	7.613	<0.001
F/T	8.094	11.400	21.802		
p	<0.001	<0.001	<0.001		

Note: ☆: every two groups compare $p < 0.001$.

3.2. Effect of FNS Combined with Psycho-cardiology Treatment on TNF- α in Patients with SCAD and Depression

The concentrations of serum tumor necrosis factor-α (TNF-α) in the three groups were analyzed before and after treatment. Intra group comparison: The concentration of serum TNF-α decreased after treatment, and the difference was statistically significant in control group, psycho-cardiology treatment group and combined treatment group($p<0.05$). Inter group comparison: Before treatment, there was no significant difference among the control group, the psycho-cardiology treatment group and the combined treatment group($p>0.05$). After treatment, the serum TNF-α in the combined treatment group decreased most obviously, and the difference was statistically significant ($p<0.05$). See Table 2.

Table 2. *Comparison of TNF-α in three groups before and after treatment and between groups(pg/ml).*

Variable	Control group(n=50)	psycho-cardiology treatment group(n=50)	Combined treatment group(n=50)	F/T	P
TNF- αBefore treatment	3.87±0.39	3.72±0.47	3.73 ±0.35	1.894	0.154
TNF- α After treatment	3.63±0.48☆	3.51±0.49△	3.21 ±0.39 ☆△	26.322	<0.001
F/T	2.680	2.286	7.056		
P	0.009	0.024	<0.001		

Note: ☆: every two groups compare $p<0.001$.

3.3. The Effect of FNS Combined with Psycho-Cardiology Treatment on 5-HT and DA in Patients with SCAD and Depression

The serum 5-hydroxytryptamine (5-HT) and dopamine (DA) of the three groups were analyzed before and after treatment. Intra group comparison: There was no significant difference in the control group before and after treatment ($p>0.05$). But the concentrations of 5-HT and DA in the psycho-cardiology treatment group and the combination treatment group increased significantly after treatment ($p<0.05$). Inter group comparison: The levels of serum 5-HT and DA in the combined treatment group were higher than those in the control group and psycho-cardiology treatment group, and the difference was statistically significant ($p < 0.05$). See Table 3 and Table 4.

Table 3.*Comparison of 5-HT in three groups before and after treatment and between groups(mmol/L).*

Variable	Control group(n=50)	psycho-cardiology treatment group(n=50)	Combined treatment group(n=50)	F/T	P
5-HT Before treatment	1.21±0.17	1.20±0.25	1.19±0.16	0.075	0.929
5-HTAfter treatment	1.20±0.05☆	1.30±0.07☆	1.44±0.22☆	36.557	<0.001
F/T	0.395	-2.507	-6.16		
P	0.693	0.014	<0.001		

Note: ☆: every two groups compare $p < 0.001$.

Table 4. Comparison of DA in three groups before and after treatment and between groups(pg/ml)

Variable	Control group(n=50)	psycho-cardiology treatment group(n=50)	Combined treatment group(n=50)	F/T	P
DA Before treatment	2.41±0.25	2.47±0.23	2.49±0.20	1.677	0.191
DA After treatment	2.37±0.16☆	2.58±0.09☆	2.71±0.22☆	48.554	<0.001
F/T	0.741	-3.163	-5.095		
P	0.461	0.002	<0.001		

Note: ☆: every two groups compare $p < 0.001$

3.4. The Effect of FNS Combined with Psycho-cardiology Treatment on HAMD Scores of Patients with SCAD and Depression

The HAMD scores of the three groups before and after treatment were compared. Intra group comparison: there was no significant difference in the control group before and after treatment($p>0.05$), but the score in the psycho-cardiology treatment group and the combined treatment group decreased significantly after treatment($p<0.05$). Inter group comparison: there was no significant difference among the three groups before treatment ($p>0.05$). After treatment, the HAMA score in the combined treatment group was significantly lower than that in the control group and the psycho-cardiology treatment group($p<0.05$). See Table 5.

Table 5. Comparison of HAMD in three groups before and after treatment and between groups.

Variable	Control group(n=50)	psycho-cardiology treatment group(n=50)	Combined treatment group(n=50)	F/T	P
HAMD Before treatment	27.72 ±2.35	27.14 ±1.90	27.80 ±1.89	1.523	0.221
MAMD After treatment	27.26 ±2.17☆	19.70 ±2.11☆	12.72 ±1.24☆	738.645	<0.001
F/T	1.051	18.494	47.013		
P	0.313	<0.001	<0.001		

Note: ☆: every two groups compare $p < 0.001$.

4. Discussion

Today, with the rapid development of economy, science and technology, SCAD is still one of the most popular diseases in the world. It has been concerned by the medical profession because of its high morbidity, mortality and medical expenses. The main clinical manifestation of SCAD is angina pectoris. Pain occurs not only in the precordium, but also in the left shoulder, medial left arm, ring finger, little finger, neck, pharynx, mandible and so on. Because of its different degree of pain, changeable forms of expression and serious consequences, it often causes patients' fear, depression and other bad emotions. For a long time, the relationship between psychology, body and heart disease has attracted the attention of experts in various fields. Clinical scientists recorded the correlation between psychological disorders and SCAD as early as 1973. An increased risk of cardiovascular death was observed in patients with depression [9]. Farquhar JM et al reported that the prevalence of depression in people with SCAD was as high as 15%-30% [23-24]. Gao Yang et al reported that among patients hospitalized due to SCAD, the incidence of depressive symptoms was as high as 46.6% [5]. Therefore, depression has been used as an independent risk factor for SCAD to predict major adverse cardiac events [25].

Brain natriuretic peptide (BNP) is mainly secreted by ventricular myocytes and affected by ventricular filling. Its main functions are natriuretic excretion, diuresis and vasodilation.

Although NT-proBNP and the precursors of BNP have the same molar number in blood, they do not have biological activity. NT-proBNP and BNP are both recognized as sensitive indicators of cardiac function. The relative change of NT-proBNP level at discharge and hospitalization is a strong predictor of rehospitalization or death in patients with heart failure [26]. TNF-α is produced by activated monocytes or macrophages and is associated with adverse effects such as vascular endothelial activation, atherosclerotic plaque formation, rupture and impaired cardiac function. In a large study of healthy adults, individuals with depression have higher levels of C-reactive protein, TNF-α, IL-6, homocysteine and fibrinogen [27]. In this study, the levels of NT-proBNP and TNF-α in the three groups were significantly increased before treatment, owing to the face that long-term coronary artery stenosis induced the decrease of oxygen supply to cardiomyocytes and the increase of ventricular end-diastolic volume, inflammatory factors, and NT-proBNP. After psychological intervention combined with conventional treatment of SCAD, the serum levels of NT-proBNP and TNF-α in the psycho-cardiology treatment group were significantly lower, which were better than that in the control group. Previous studies also showed that psycho-cardiology treatment can effectively improve the prognosis of patients [28-29]. The results of this experiment were as same as those of previous studies. In addition, this study showed that the combined treatment, which were given FNS on the basis of conventional treatment of SCAD and psychological intervention, has a more significant effect on serum NT-proBNP and TNF-α. The possible reason is that FNS can improve myocardial ischemia and prognosis by regulating autonomic nervous function and inhibiting inflammatory reaction [30]. Basic studies also showed that FNS in post-stroke depression rats can effectively reduce the expression of IL-6, IL-1 β and TNF-α [21]. And it was confirmed by Wang M et al that FNS can up-regulate the expression of micro-29c, and then reduce the expression of tumor necrosis factor receptor-1 and inflammatory cytokines to produce antidepressant effect [31].

HAMD is widely used in clinical diagnosis in screening for depression with good reliability and validity. There are HAMD-17, HAMD-21 and HAMD-24. HAMD-24 was used in this experiment. In this study, after psycho-cardiology treatment combined with conventional treatment of SCAD, the HAMD scores of patients were significantly lower than that of the control group, and the results of this study were the same as those of previous studies [21]. However, on the basis of the above treatment, we found that the addition of FNS could more effectively reduce the HAMD scores and improve the depressive symptoms of patients. The specific reason is not completely clear, which may be related to the regulation of neurological function after FNS. Through the biological model, we know that the nerve fibers emitted from cerebellar fastigial nucleus eventually produce biological effects through regulating the sympathetic nerve and vagus nerve [32-33]. It has a long history to improve depression by regulating vagus nerve function. Hein et al confirmed for the first time that percutaneous auricular vagus nerve stimulation could effectively improve depression in patients through randomized trials [34]. D'Urso G et al [35] confirmed that vagus nerve stimulation could improve epilepsy, depression, disorder and dementia through clinical studies. The specific mechanism reported by Cimpianu CL et al is attributed to the fact that vagus nerve stimulation can regulate many brain regions related to emotion and physical and mental feelings, including locus coeruleus, amygdala, hippocampus and so on [36].

5-HT is a monoamine neurotransmitter, also known as serotonin. It is mainly secreted by 5-HT neurons and stored in peripheral nerve vesicles. The peripheral vesicles release 5-HT into the synaptic space by stimulation. After contacting with the corresponding receptors in the postsynaptic membrane, some of them dissociates rapidly. But most of them are reabsorbed into the presynaptic membrane by 5-HT pumps. Reduce of release of 5-HT is considered to be the pathophysiological basis of depression [37]. Detecting the content of 5-HT in peripheral serum is a convenient and effective method to reflect the content of center [37]. SSRI can inhibit 5-HT receptor in synapse, reduce 5-HT reuptake and increase the content of 5-HT in synaptic space, thus producing antidepressant effect [38]. A recent meta-analysis by Fernandes N et al has demonstrated that SSRI is associated with a significantly lower risk of myocardial infarction in patients with SCAD and depression (RR 0.54, 95% CI 0.34-0.86) [39]. Previous studies show that FNS can effectively increase the content of 5-HT in serum [40]. In this study, after psychological intervention, it can effectively increase the level of serum 5-HT of patients, suggesting that it can improve the depression of patients. After intervention with FNS, the level of 5-HT in serum of the patients is further increased, suggesting that the combined treatment plays a more significant role in antidepressant effect. In addition, the results of this study show that the combination of FNS can effectively increase the content of DA in serum and further produce antidepressant effect, but its specific mechanism needs to be further studied. Basic studies have confirmed that FNS can effectively increase the content of 5-HT in both cerebral hemispheres of rats, which may be caused by the joint action of neural loop and humoral regulation [41]. FNS can improve behavior and mental activity by increasing the level of cAMP response area of neurons, up-regulating brain-derived neurotrophic factor, and promoting the synthesis of monoamine transmitters such as 5-HT and DA in hippocampal and prefrontal cortex neurons. Huguet G et al [42] suggest that the antidepressant effect after electrical stimulation may be related to the decreased activity of c-Fos neurons. Our animal experiments show that FNS can increase the content of 5-HT in the brain tissue, and that 5-HT can reduce the excitability of central sympathetic nerve and regulate arterial baroreflex, thus reducing sudden cardiac death [15].

In addition, the occurrence and development of depression

and SCAD are related to autonomic nervous dysfunction. The cardiac nervous system is innervated by both parasympathetic and sympathetic nerves. Under the action of the two nerves, the heart can make adaptive changes to emotional factors such as stress [43]. Some studies have confirmed that sympathetic excitation and parasympathetic inhibition are always present in patients with SCAD [44].

Autonomic nervous dysfunction can increase mortality in patients with acute myocardial infarction. In patients with heart disease combined with depression, the autonomic nervous balance changes to the increase of sympathetic activity. As we all know, HRV is an effective indicator of vagal tension, and some studies have found that there is a linear relationship between the decrease of HRV and the severity of depression. In other words, with the decrease of HRV, depressive symptoms may worsen [45]. Runfeng Zhang et al studied the effect of FNS on HRV by establishing a rat myocardial infarction model, and confirmed that FNS could improve HRV parameters [13]. After SCAD patients accepted the treatment of FNS, the levels of standard deviation of the NN intervals, standard deviation of mean NN intervals in 5-minute recordings, square root of the mean squared differences of successive NN intervals, total power and high frequency power (HF) in the experimental group were significantly higher than those in the control group. The decrease of low frequencypower (LF) and LF/HF suggested that FNS could decrease the sympathetic nerve activity and increase the vagus nerve activity in SCAD patients, thus improving the cardiac autonomic nerve function in SCAD patients [16]. Therefore, we speculate that FNS combined with psychological intervention may also improve the prognosis of patients with SCAD complicated with depression by improving vagus nerve tension.

5. Conclusion

Psycho-cardiology treatment combined with FNS can effectively reduce the level of serum inflammatory factors in patients with SCAD complicated with depression and increase the level of serum 5-HT and DA, which can improve depressive symptoms and may improve the prognosis of patients.

Abbreviations

FNS	Fastigial Nucleus Stimulation
BNP	Brain Natriuretic Peptide
NT-proBNP	N-terminal pro-B type Natriuretic Peptide
5-HT	5-hydroxytryptamine
DA	Dopamine
SCAD	Stable Coronary Artery Disease
TNF-α	Tumor NecrosisFactor-α
HAMD	Hamilton Depression Scale
SSRI	Selective Serotonin ReuptakeInhibitor
HRV	Heart Rate Variability
HF	High Frequency Power
LF	Low Frequency Power

Author Contributions

Heng Zhang: Formal Analysis, Conceptualization, Investigation, Writing-original draft, Methodology

Binxia zhu: Writing - review & editing

Runfeng Zhang: Conceptualization, Methodology, Supervision, Project administration

Conflicts of Interest

The authors declare no conflicts of interest.

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Biography

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Research Field

Heng Zhang: Cerebellar fastigial nucleus electrostimulation, Chronic heart failure, post-infarction, malignant arrhythmia inducibility, neurotransmitter release

Binxia Zhu: coronary heart disease, myocardial regeneration medicine, artemisinin effect for dilated cardiomyopathy, post-infarction, malignant arrhythmia inducibility

Runfeng Zhang: psycho–cardiology, brain science, brain–heart interactions, brain intervention research for coronary heart disease, myocardial regeneration medicine