Original Article
Effects of angiotensin converting enzyme inhibitors on cognitive functions in patients with chronic heart failure

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Abstract: Background and Aims: Twenty to eighty percent of the patients with chronic heart failure (CHF) were combined with cognitive impairment (CI). Effective treatment of CHF could, to some extent, reverse CI. The aim of this study is to investigate the effects of angiotensin converting enzyme inhibitors (ACEI) on cognitive functions in CHF patients. Methods: One hundred and fifty-nine newly diagnosed patients with CHF at Cardiology Department and Neurology Department of Jinan Central Hospital were subjected to the mini mental state examination (MMSE). Eighty-one CHF patients combined with CI were divided into the ACEI group (50 cases, with ACEI treatment) and the control group (31 cases, without ACEI treatment). The patients were followed up 6 months after the treatment and subjected to MMSE again. Results: Out of the 159 newly diagnosed CHF patients, 81 (50.9%) were combined with CI. As to these 81 patients, the total scores as well as the scores for orientation, memory, attention, calculative ability and language functioning in the ACEI group were all significantly higher than those in the control group (P<0.05) after treatment. In the ACEI group, the total scores as well as the scores for memory, attention, calculative ability and language ability determined after treatment were all significantly higher than those determined before treatment (P<0.05). Conclusions: About half of the CHF patients were combined with CI, which involves multiple cognitive domains. ACEI can improve cognitive functions in CHF patients in orientation, memory, attention, calculative ability and language functioning.

Keywords: Angiotensin converting enzyme inhibitors, cognitive function, chronic heart failure

Introduction

Chronic heart failure (CHF) is a clinical syndrome caused by impaired ventricular filling and ejection as a result of cardiac structural abnormalities or functional disorders. The cognitive domains include memory, attention, orientation, calculation, analysis, understanding, judgment, visual-spatial ability, executive capacity, etc. Cognitive impairment (CI) is defined as a decline in at least one of these cognitive domains. CHF and CI are common in the elderly patients [1]. Both CHF and CI can lead to high morbidity and mortality rates and decrease quality of life. Twenty to eighty percent of the patients with CHF also suffer from CI. The risk of CI in CHF patients is 4 times higher than that in the healthy people [2]. CI can affect the activity of daily living of CHF patients and lead to poor compliance to standard treatment of these patients. It has been reported that the heart failure severity assessed by New York Heart Association (NYHA) functional class was positively correlated with the extent of CI [3]. Left ventricular ejection fraction (LVEF) was associated independently with CI [4, 5]. The gender, age, education level, depression status, the blood glucose values, the blood pressure, drinking, smoking and the presence or absence of atrial fibrillation do not affect the correlation between CHF and CI. However, there has been no large-scale epidemiological survey of cognitive functions in CHF patients in China.

Effective treatment of CHF could improve cognitive functions [6]. CHF could lead to disorders of the neuroendocrine system including the activation of renin-angiotensin-aldosterone system (RAAS) and adrenergic system, which may affect the cognitive functions of the patients [7-10]. Angiotensin converting enzyme inhibitors (ACEI) can be used in the treatment of

Table 1. The clinical characteristics of the patients in the control group and the ACEI group

Parameter	The control group (n=31)	The ACEI group (n=50)	Test statistic value	P value
Age (mean ± SEM)	81.03±5.15	80.80±5.66	T=0.186	0.853
Gender			X^2=0.653	0.419
Male	12 (38.7%)	15 (30.0%)		
Female	19 (61.3%)	35 (70.0%)		
Hypertension			X^2=0.418	0.518
Yes	22 (71.0%)	32 (64.0%)		
No	9 (29.0%)	18 (36.0%)		

Note: ACEI, angiotensin converting enzyme inhibitors.

patients with CHF and significantly improve the prognosis of these patients. Since ACEI could regulate the renin-angiotensin system and the endothelial system [8], the effects of ACEI on cognitive functions in CHF patients have aroused much attention. However, there has been no relevant research in CHF patients in China. In this study, the effects of ACEI on cognitive functions in CHF patients were investigated. ACEI could improve cognitive functions in CHF patients in orientation, memory, attention, calculative ability and language functioning.

Materials and methods

Patients

This study was approved by the Ethics Committee of Jinan Central Hospital Affiliated to Shandong University. The medical records of newly diagnosed CHF patients at Cardiology Department and Neurology Department of Jinan Central Hospital from December 2011 to December 2013 were collected. CHF was diagnosed by history, physical examination, laboratory examination, etc. from a specialist in cardiovascular medicine. The including criteria for the patients to enter this study were: 1) the patients with NYHA functional class III and LVEF less than 45%, 2) with education level above primary, 3) with voluntary participation and good compliance to this study. The excluding criteria were: 1) the patients with significant neurological disorders such as Alzheimer's disease, Parkinson's disease, stroke, etc. 2) with serious mental illness such as schizophrenia, depression, etc. 3) with severe liver and kidney dysfunction, atrial fibrillation or cancer, 4) with a history of head trauma leading to loss of consciousness for more than 10 min, 5) with other diseases such as aphasia, hearing impairment, etc. affecting the evaluation of cognitive function. One hundred and fifty-nine patients were enrolled in this study. Seventy patients were males and 89 were females. The median age was 77.84±6.97 years. Written informed consent was obtained from all the patients.

The mini mental state examination (MMSE)

The enrolled 159 patients were subjected to MMSE. MMSE is a 30-point questionnaire test that is used to measure cognitive functions, which has a maximal score of 30. In MMSE, the measured functions include orientation, calculation, memory, and attention, language functioning and visual-spatial ability. The score lower than or equal to 17 for the patient who is illiterate, 20 for the patient with primary education or 24 for the patient with middle education or above indicates CI. In this study, the education level of each enrolled patient was above primary. Thus, the score higher than 24 indicated normal cognitive functions and the score lower than or equal to 24 indicated CI. Out of the 159 patients, 81 were identified as CI.

These 81 patients were divided into the ACEI group (15 males, 35 females; median age, 80.80±5.66 years) and the control group (12 males, 19 females; median age, 81.03±5.15 years). The clinical data of these patients were shown in **Table 1**. The patients were followed up 6 months after the treatment and subjected to MMSE again.

Treatment

In the control group, the patients received conventional treatment including antihypertensive therapy, oxygen therapy, diuretic therapy, cardiac treatment, relieving spasm and asthma, anti-infection treatment, etc. In the ACEI group, the patients received both conventional treatment mentioned above and ACEI drugs (Fosinopril, 10 mg orally 1 time a day). The patients in the ACEI group had not received ACEI drugs orally or received ACEI drugs for less than a month before this study. During the 6 months period of treatment, the patients who replaced or added other antihypertensive drugs were censored.

Table 2. The total MMSE scores as well as the scores in the control group and the ACEI group before treatment (mean ± SEM)

	The control group (n=31)	The ACEI group (n=50)	T value	p value
Orientation	7.90±1.08	8.06±1.06	-0.644	0.521
Memory	2.19±1.08	2.24±1.02	-0.195	0.846
Attention and calculative ability	2.58±1.63	2.54±1.57	0.112	0.911
Recall	1.68±1.08	1.84±1.02	-0.684	0.496
Language functioning	6.74±0.96	6.62±0.95	0.560	0.577
Total	21.10±3.49	21.30±3.23	-0.267	0.790

Note: MMSE, the mini mental state examination; ACEI, angiotensin converting enzyme inhibitors.

Table 3. The total MMSE scores as well as the scores before and after treatment in the control group (mean ± SEM, n=31)

	Before treatment	After treatment	T value	p value
Orientation	7.90±1.08	7.68±1.22	0.705	0.486
Memory	2.19±1.08	1.94±0.81	1.017	0.317
Attention and calculative ability	2.58±1.63	2.97±1.72	-0.836	0.410
Recall	1.68±1.08	1.58±0.99	0.356	0.724
Language functioning	6.74±0.96	6.61±0.80	0.559	0.580
Totla	21.10±3.49	20.77±2.47	0.422	0.676

Note: MMSE, the mini mental state examination.

Statistical analysis

All data were processed using SPSS17.0 statistical package and were expressed as mean ± standard error of mean (SEM). Normally distributed continuous variables were analyzed using t test. Non-normally distributed continuous variables were analyzed using Mann-Whitney U test. Count data were analyzed using r test. *P*-values of less than 0.05 were considered statistically significant.

Results

Evaluation of cognitive functions in CHF patients before treatment

To evaluate the cognitive functions in CHF patients, the MMSE was performed. Out of the 159 newly diagnosed CHF patients, 81 patients (50.9%) with MMSE score less than 24 were identified as CI. These 81 patients were divided into the ACEI group and the control group. The patients in the ACEI group had not received ACEI drugs orally or received ACEI drugs for less than a month before this study. As shown in **Table 1**, there were no significant differences in age, gender and the blood pressure between these two groups. As shown in **Table 2**, there were no significant differences between the control group and the ACEI group in the total MMSE scores, as well as the scores for orientation, memory, attention and calculative ability, recall and language functioning before treatment.

ACEI treatment improves cognitive functions in CHF patients

In the control group, the patients received conventional treatment without ACEI drugs. In the ACEI group, the patients received both conventional treatment and ACEI drugs (Fosinopril, 10 mg orally 1 time a day). The patients were followed up 6 months after the treatment and subjected to MMSE again. In the control group, there were no significant differences before and after treatment in the total MMSE scores, as well as the scores for orientation, memory, attention and calculative ability, recall and language functioning (**Table 3**).

In the ACEI group, the total MMSE scores as well as the scores for attention and calculative ability, memory and language functioning after treatment were all significantly higher than those before treatment (*P*<0.01). There were no significant differences before and after treatment in the scores for orientation and recall (**Table 4**). After treatment, the total MMSE scores as well as the scores for orientation, attention and calculative ability, memory and language functioning in the ACEI group were all significantly higher than those in the control group (*P*<0.01). There was no significant difference between the control group and the ACEI group in the score for recall (**Table 5**). These results indicate that ACEI can improve cognitive functions in CHF patients in orientation, memory, attention, calculative ability and language functioning.

Table 4. The total MMSE scores as well as the scores before and after treatment in the ACEI group (mean ± SEM, n=50)

	Before treatment	After treatment	T value	p value
Orientation	8.06±1.06	8.26±0.60	-1.400	0.168
Memory	2.24±1.02	2.86±0.50	-4.109	0.000**
Attention and calculative ability	2.54±1.57	4.52±0.91	-9.753	0.000**
Recall	1.84±1.02	1.62±0.49	1.562	0.125
Language functioning	6.62±0.95	7.12±0.80	-2.793	0.007**
Totla	21.30±3.23	24.38±2.49	-8.957	0.000**

Note: MMSE, the mini mental state examination; ACEI, angiotensin converting enzyme inhibitors. **$P<0.01$.

Table 5. The total MMSE scores as well as the scores in the control group and the ACEI group after treatment (mean ± SEM)

	The control group (n=31)	The ACEI group (n=50)	T value	p value
Orientation	7.68±1.22	8.26±0.60	-2.477	0.018*
Memory	1.94±0.81	2.86±0.50	-5.704	0.000**
Attention and calculative ability	2.97±1.72	4.52±0.91	-4.634	0.000**
Recall	1.58±0.99	1.62±0.49	-0.206	0.838
Language functioning	6.61±0.80	7.12±0.80	-2.771	0.007**
Totla	20.77±2.47	24.38±2.49	-6.352	0.000**

Note: MMSE, the mini mental state examination; ACEI, angiotensin converting enzyme inhibitors. *$P<0.05$, **$P<0.01$.

Discussion

CHF and CI are common in the elderly patients. In this study, the cognitive functions in CHF patients were examined and the effects of ACEI on cognitive functions in CHF patients were investigated. CHF patients are difficult to focus attention, easily impatient and irritable. The MMSE is a valid and reliable questionnaire for cognitive function measurement with short administration period. Thus in this study, the MMSE was performed to evaluate the cognitive functions in CHF patients.

A cross-sectional survey in Italy showed that the risk of CI was significantly greater in the CHF patients than those without history of CHF [11]. Furthermore, the decline of the cognitive functions was more rapid in CHF patients [7, 12]. In the elderly patients, CHF is often accompanied by a variety of diseases which may also affect the cognitive functions. Therefore, the patients with significant neurological disorders, serious mental illness, severe liver and kidney dysfunction, atrial fibrillation or cancer were excluded in this study to avoid the affecting of these diseases to the cognitive functions of CHF patients. As to the elderly CFH patients, if the condition is too severe, it is hard for them to complete the study. Thus the CHF patients with NYHA functional class III were chosen to participate in this study. Out of the 159 newly diagnosed CHF patients, 81 patients with MMSE score less than 24 were identified as CI. The incidence of CI in CHF patients was 50.9% which was significantly higher than that in the normal population, as reported in the literatures [13].

The impaired cognitive domains in CHF patients included executive function, memory, attention, language functioning, psychomotor speed, etc. [5]. A study involving 414 participants showed that significantly more HF patients (24%) had deficits in three or more cognitive domains. The most common deficit was poorer memory, followed by decreased psychomotor speed and executive function. Higher HF severity, as well as older age, was associated with more cognitive deficits [14]. Accordingly, our results also indicate that the CI in CHF patients involves multiple domains, including orientation, memory, attention, calculative ability, recall and language functioning.

The results in this study indicate that ACEI drugs can improve cognitive functions in CHF patients in orientation, memory, attention, calculative ability and language functioning. While the effects of ACEI on recall remains further investigation. A study with small sample size showed ACEI drugs could improve cerebral perfusion in CHF patients [15]. Long-term administration of ACEI drugs in rats could significantly improve the spatial memory and this might be associated with increased cerebral perfusion. Eighteen months of treatment with a low dose

of the ACEI drug in the Dahl salt-sensitive rats could improve their memory function in a dose dependent manner. This improvement was associated with significant increases in hippo-campal CA1 cells and capillary densities in the CA1 regions [16]. Furthermore, treatment with ACEI selectively improved cognitive perfor-mance in patients with heart failure [17]. Altogether, these results indicate that ACEI drug could improve the cognitive functions of CHF patients. However, we do not know wheth-er the improvement was due to ACEI drug treat-ment only. Further investigation on the associa-tion of CHF and cognitive functions, as well as the effects of various interventions on the improvement of cognitive functions will provide new strategies for the prevention and treat-ment of CI.

Disclosure of conflict of interest

None.

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