Biomedical Research 2016; 27 (3): 912-916 *ISSN 0970-938X*
www.biomedres.info

A clinical trial investigating the effect of trimetazidine combined with oxiracetam in patients with vascular dementia.

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Abstract

The aim of this study is to elucidate the efficiency and safety of Trimetazidine (TMZ) combined with oxiracetam in treating patients with Vascular Dementia (VD). From January 2013 to January 2015, 82 patients with VD were randomly assigned to a test and control group (41 cases each). In addition to the same basic medicine, oxiracetam was administered to the control group at a dose of 0.8 g, 3 times a day. Furthermore, in addition to the base treatment, TMZ was administered to the test group at a dose of 20.0 mg, 3 times a day for the 90-day treatment period. The cognitive function was measured before and after treatment by using the Mini-Mental State Examination Scale (MMSE), Clinical Dementia Rating Scale (CDR), and Barthel Index (BI) assessment while adverse reactions were also monitored. After treatment, the MMSE and BI scores (20.67 ± 4.01 and 80.29 ± 7.42, respectively) increased significantly in the test group compared with that of the control group (17.78 ± 3.55 and 71.04 ± 8.03, respectively). The CDR score (1.69 ± 0.35) decreased significantly in the test group compared with that in the control group (2.03 ± 0.27, P<0.01). Furthermore, obvious adverse reactions were not found in either group. The combined effect of TMZ and oxiracetam in the treatment of VD was better than that of the placebo and showed an excellent safety profile.

Keywords: Vascular dementia, Trimetazidine, Oxiracetam.

Accepted on March 03, 2016

Introduction

Vascular Dementia (VD) is a syndrome consisting of intelligence and cognitive dysfunction caused by cerebral tissue damage induced by cerebrovascular disease. The quality of life of patients with VD is severely affected. Drugs such as anticholinesterase and those that improve microcirculation are used to treat VD, but they have poor efficacy. Trimetazidine (TMZ) can improve the generation rate of Adenosine Triphosphate (ATP) to optimize energy metabolism, which inhibits 3-keto acyl coenzyme, a sulfur enzyme and depresses the oxidation of β-fatty acid, increases glucose oxidation, and reduces intracellular acidosis.

Previous research studies [1-5] showed that TMZ decreased the overload of intracellular H^+, Na^+, and Ca^{2+} and depressed the production of oxygen free radical by antioxidant effects. Furthermore, TMZ prevented oxidative changes induced in a rat model of a sporadic type of Alzheimer's disease, was anti-apoptotic, did not affect the hemodynamics, protected vascular endothelial function, and reduced the inflammatory process. In addition, TMZ improved the activity of free radical scavenging enzymes, inhibited the peroxidation of oxygen free radicals on membrane lipid, stabilized various membrane structures within the cell, reduced the leakage of enzymes in the cell and the accumulation of calcium in the mitochondria, maintained mitochondrial function, and inhibited inflammatory factors release and apoptosis of nerve cells [6]. TMZ also reduced the area of cerebral infarction and brain cell edema [6].

Oxiracetam promoted the metabolic activity of brain cells and improved disturbances in memory and intelligence functions [7,8]. Previous studies found that the treatment of VD with oxiracetam improved the condition [9,10]. Although studies on the curative effects of TMZ in acute coronary syndrome have been carried out, there are no available reports of clinical trials on its use for treating VD. Therefore, the present study describes a clinical trial investigating the curative effects of TMZ combined with oxiracetam in the treatment of patients with VD. We aim to demonstrate the safety and efficiency of combination therapy with TMZ and oxiracetam in the treatment of VD.

Material and Methods

Subjects

A total of 82 cases of out-patients with VD were selected from the No.2 Hospital of Baoding Hospital, from January 2013 to January 2015 consisting of 46 and 36 men and women aged 56-78 years with an average age of 67.6 ± 6.1 years. There were 66 patients with cerebral infarction aged 2-7 years with an average age of 4.5 ± 2.4 years, 14 patients with cerebral hemorrhage aged 2-8 years with an average age of 5.1 ± 2.8 years; and 2 patients with subarachnoid hemorrhage were 3-4 years. They are randomly divided into test group and control group according to the random number table method. The 41 test group cases consisted of 24 and 17 male and female patients, respectively with an average age of 68.8 ± 6.6 years. Furthermore, 33 of the patients had cerebral infarction and were aged 2-7 years with an average age of 4.6 ± 2.2 years, 7 had cerebral hemorrhage and were aged 2-8 years with an average of 5.2 ± 2.7 years, and 1 patient aged 4 years had subarachnoid hemorrhage. The 41 control cases consisted of 22 and 19 male and female patients, respectively with a mean age of 66.7 ± 7.2 years. In addition, 33 patients in this group had cerebral infarction and were aged 2-7 years with an average age of 4.4 ± 2.5 years, 7 had cerebral hemorrhage and were aged 2-7 years with an average age of 5.0 ± 2.6 years, and 1 patient aged 3 years had subarachnoid hemorrhage. The patient characteristics including culture degree, occupation, smoking and drinking history, complications, Mini-Mental State Examination (MMSE) score, Clinical Dementia Rating Scale (CDR), daily living activities, and Barthel Index (BI) were not significantly different between the groups (P>0.05). This study is approved by the hospital ethics committee of the No.2 Hospital of Baoding, family members of the patients signed informed consent.

Diagnostic and exclusion criteria

Diagnostic criteria: The following standards were used to confirm the diagnosis of VD. (1) The Diagnostic and Statistical Manual of the American Society of Mental Illness, mental disorder's standard [11]; (2) clinical dementia symptoms such as mental retardation, slow response, MMSE score <26 points, and Hachinski ischemic scale >8 points; (3) cerebral vascular lesions were determined using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scanning, which confirmed that the dementia had occurred within 3 months of the study onset without other organ dysfunctions.

Exclusion criteria: Patients who showed evidence of the following conditions were excluded. (1) Other causes of dementia; (2) disturbance of consciousness, mental disease, and metabolic disease history; (3) the use of other drugs that could interference with the evaluation such as donepezil, huperzine, memantine, and piracetam; (4) allergies to TMZ and oxiracetam; and (5) allergies to sunset yellow FCF S (E110) and carmine (E124).

Treatment of patients

The oral treatment route was used while parameters and treatment-related effects including anti-platelet aggregation, improved microcirculation, brain cell nutrition, regulation of blood pressure, and blood glucose and lipid, were monitored in the two groups. The control group was treated with oxiracetam (Shiyao Group Ouyi Pharmaceutical Co., Ltd, Approval No. H20031033), consisting of 0.4 g/piece administered at a dose of 0.8 g taken 3 times a day after meals for the 90-day treatment period. The test group was treated with oxiracetam at the same dosage as that of the control group, which was combined with 20-mg TMZ dihydrochloride tablets (Beijing Wansheng Pharmaceutical Co., Ltd, Approval No. H20065167) administered at a dose of 20 mg 3 times a day with meals for the 90-day treatment period.

Observational indicators

The MMSE, CDR, and BI were evaluated before and on day 90 after treatment.

Safety assessment

The safety assessment involved detecting the liver and kidney functions of the patients before and on day-90 after treatment.

Statistical analysis

All the statistical tests used in data analysis used a double-sided inspection and a P<0.05 was considered statistically significant. The data are presented as the mean ± Standard Deviation (SD) for all statistical descriptions. The multiple follow-up index used a repeated measures design for the analysis of variance (ANOVA), and a paired t-test was used to compare each time point between the two groups. The counted parameters were expressed using the frequency (constituent ratio) as the statistical descriptor, and the χ^2 test was used to compare both groups.

Results

MMSE

The comparison of the MMSE scores between the test and control groups before and after treatment is shown in Table 1. After the 90 days, the MMSE scores increased more significantly in the test group than they did in the control group and were higher than they were before treatment (P<0.01).

Table 1. *Comparison of MMSE scores between the two groups before and after treatment ($\bar{x}$ ± s: mean ± standard deviation).*

Groups	n	Before treatment	90 days after treatment	t	p

Test group	41	14.18 ± 4.34	20.67 ± 4.01	t_3=7.031	P_3<0.001
Control group	41	14.31 ± 4.62	17.78 ± 3.55	t_4=3.814	P_4<0.01
-	-	t_1=0.131, P_1>0.05	t_2=3.457, P_2<0.01	-	-

Annotation: t_1 and P_1: comparison of the two groups before treatment. t_2 and P_2: comparison of the two groups after treatment. t_3 and P_3: comparison before and after treatment in the test group. t_4 and P_4: comparison before and after treatment in the control group.

CDR

The comparison of the CDR of the two groups before and after treatment is shown in Table 2. After 90 days, the CDR scores of the test group decreased more significantly than those of the control group did and were lower than they were before treatment (P<0.01).

Table 2. *Comparison of CDR between the two groups before and after treatment ($\bar{x}$ ± s: mean ± standard deviation).*

Groups	n	Before treatment	90days after treatment	t	p
Test group	41	2.51 ± 0.50	1.69 ± 0.35	t_7=8.604	P_7<0.001
Control group	41	2.46 ± 0.38	2.03 ± 0.27	t_8=5.890	P_8<0.01
-	-	t_5=0.510, P_5>0.05	t_6=4.928, P_6<0.01	-	-

Annotation: t_5 and P_5: comparison of the two groups before treatment. t_6 and P_6: comparison of the two groups after treatment. t_7 and P_7: comparison before and after treatment in the test group. t_8 and P_8: comparison before and after treatment in the control group.

BI

The BI was compared between the two groups before and after treatment, and the result is shown in Table 3. After 90 days, the BI scores of the test group increased more significantly than those of the control group did, and were higher than they were before treatment (P<0.01).

Table 3. *Comparison of BI scores between the two groups before and after treatment ($\bar{x}$ ± s: mean ± standard deviation).*

Groups	n	Before treatment	90days after treatment	t	p
Test group	41	57.65 ± 9.71	80.29 ± 7.42	t_{11}=11.860	P_{11}<0.001
Control group	41	57.89 ± 9.24	71.04 ± 8.03	t_{12}=6.878	P_{12}<0.01
-	-	t_9=0.115, P_9>0.05	t_{10}=5.416, P_{10}<0.01	-	-

Annotation: t_9 and P_9: comparison of the two groups before treatment. t_{10} and P_{10}: comparison of the two groups after treatment. t_{11} and P_{11}: comparison before and after treatment in the test group. t_{12} and P_{12}: comparison before and after treatment in the control group.

Table 4. *Comparison of cases of Liver function abnormal between the two groups before and after treatment.*

Groups	n	Before treatment	90 days after treatment	χ^2	p
Control group	41	1	3	0.21	>0.05
Test group	41	1	4		

Adverse reactions

The two groups of patients showed stability in the parameters determining the quality of life over the course of the treatment. There were no deleterious effects such as liver and kidney dysfunction and allergy. There was no significant difference in the nausea and stomach discomfort experienced by patients in both groups after the treatment (test and control groups, 4 and 3 cases, respectively, χ^2=0.21, P>0.05, Table 4).

Discussion

VD seriously affects the patient's cognition, social activities, and ability to perform activities of daily life. These VD-induced effects are related to phenomenon such as the reduction of cerebral blood flow, damage to the cholinergic function, decreased cerebral metabolic rate, the toxicity of excitatory amino acid, and oxidative stress. Previous studies [1-3,6,12,13] showed that TMZ is a piperazine derivative that can maintain the intracellular ATP stability, limit intracellular acidosis, inhibit intracellular sodium and calcium ion aggregation, exhibit antioxidant effects by reducing the production of oxygen free radicals, reduce apoptosis, and mitigate the degree of nerve function damage. Oxiracetam is a nootropic, which promotes the synthesis of phosphorylcholine and phosphorylethanolamine and, thereby, enhances brain metabolism, increases the synthesis of protein and nucleic acid in the brain, and improves the memory and learning functions of patients [7-10].

The results of this study show that 90 days after treatment, the MMSE and BI scores of the test group increased significantly more than those of the control group did and were higher than they were before treatment ($P<0.01$). This result indicates that combination treatment with TMZ and oxiracetam improved the cognitive function and self-care ability of the patients. The CDR score of the test group decreased more significantly than that of the control group did ($P<0.01$), which illustrates that the degree of dementia in the patients was reduced. This observation is in agreement with previous relevant studies showing that TMZ and oxiracetam exhibited beneficial effects such as improved brain cell metabolism and inhibition of oxidative stress, as well as promotion of acetylcholine release and neuroprotection. Previous studies [14-19] found that TMZ reduced the infarct area in rat models, reduced the blood-brain-barrier permeability, had neuroprotective activity, increased superoxide dismutase activity and glutathione levels, and reduced lipid peroxidation and myeloperoxidase activity.

There was no significant difference in the adverse reactions observed between the two groups on day 90 after treatment. Furthermore, the results indicated that there were few side effects associated with combination TMZ and oxiracetam treatment. This study demonstrated the superior efficacy and safety of the combination of TMZ and oxiracetam over the placebo for the treatment of VD. However, the small number of patients used was a limitation of this study and, therefore, further investigations involving a larger number of cases would be necessary.

Acknowledgment

We thank the patients and their families for their participation. Thank my family.

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