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α-Lipoic acid treatment of aged type 2 diabetes mellitus complicated with acute cerebral infarction

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Abstract. – OBJECTIVE: This study aims to evaluate the efficacy and safety of α-lipoic acid in the treatment of aged type 2 diabetes mellitus (T2DM) complicated with acute cerebral infarction.

PATIENTS AND METHODS: 90 patients were randomly divided into two groups, on the basis of conventional treatment. The experiment group was administrated with α-lipoic acid, while only Vitamin C for the control group, for 3 consecutive weeks. Before and after the experiment, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and malondialdehyde (MDA) levels were measured and scored with the NIHSS (National Institutes of Health Stroke Scale), and the changes of blood glucose, insulin function and other indicators were observed.

RESULTS: After the treatment, the plasma SOD and GSH-Px levels increased, while MDA decreased ($p < 0.05$), with statistical significance when compared with the control group ($p < 0.01$). NIHSS score, blood glucose, blood lipids and HOMA-IA of the experiment group decreased significantly ($p < 0.01$); and no significant adverse reactions were found in both groups.

CONCLUSIONS: α-lipoic acid was safe and effective in the treatment of aged T2DM complicated with acute cerebral infarction, significantly reducing the patient's oxidative stress, blood glucose and lipid levels and being able to improve islet function.

Key Words:
α-lipoic acid, Type 2 diabetes mellitus, Aged, Cerebral infarction, Oxidative stress

Introduction

Diabetes is an independent risk factor for stroke. In aged patients with diabetes, the risk of stroke is 2-4 times of that in non-diabetic population with the same age. The cerebral ischemia-reperfusion neuronal apoptosis is closely related to the severity of oxidative stress[1]. α-lipoic acid is the strongest antioxidant used in clinic. It has functions including anti-oxidation, scavenging free radicals, and decreasing oxidative stress level, with exact efficacy in treatment of diabetic peripheral neuropathy and diabetic nephropathy[2,3]. Recently, some authors have used α-lipoic acid to treat traumatic brain injury, Alzheimer's disease and Parkinson's disease and have obtained good results[4]. In this study, α-lipoic acid was used for treatment of aged type 2 diabetes mellitus complicated with acute cerebral infarction. The objective is to observe the effect of α-lipoic acid on oxidative stress level, clinical symptoms, blood glucose, blood lipid and islet β-cell function in patients.

Patients and Methods

General Information

From Jan 2010 to Dec 2012, 90 aged type 2 diabetic patients, complicated with acute cerebral infarction were treated in our hospital. All patients met diagnostic criteria of WHO-1999 Diabetes, and the diagnosis of cerebral infarction also met the revised diagnostic criteria by 4th National Conference of Cerebrovascular Disease. 49 males and 41 females, aged 60-92 years, with a mean age as 71.6 years, among who 78 cases had diabetes originally, with the duration from 10 months to 23 years and the mean duration as 9.7 years, 12 cases were newly diagnosed diabetes. CT or MRI were performed and confirmed that the cases were all cerebral artery thrombotic infarction. The patients with serious heart, lung, liver, kidney, gastrointestinal diseases and mental disorders were excluded. Totally 90 patients were included and randomly divided into: Experiment Group (EG), 46 patients; Control Group (CG), 44 patients. There were no significant differences in sex, age, medical history, blood glucose, glycosylated hemoglobin, lipids, blood pressure, body mass index, liver and kidney function, infarct location and size, and the clinical symptoms between the two groups ($p > 0.05$). This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Hedong District People's Hospital. Written informed consent was obtained from all participants.

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Treatment

After the admission, lifestyle of the patients was intervened: insulin was administrated to control the blood sugar, certain drugs for anti-platelet aggregation and improving circulation. According to patients' blood lipids and blood pressure levels, antihypertensive and regulating-lipid drugs would be applied. On this basis, EG was administrated α-lipoic acid injection (Yabao Pharmaceutical Co., Ltd., Taiyuan, China), 600 mg in 250 mL 0.9% sodium chloride injection, iv gtt once per d for 3 consecutive weeks. CG was given 3.0 g Vitamin C, solved in 250 ml 0.9% sodium chloride for iv gtt injection, once per d for 3 consecutive weeks.

Observation Index

Before and after the treatment, phlebotomized and centrifuged for the for the detection of SOD, GSH-Px and MDA levels in plasma (Nanjing Jiancheng Biological Co., Ltd., Nanjing, China); during the treatment, monitored the patients' routine blood situation, blood glucose, blood lipids, blood pressure, weight, ECG, liver and kidney function, electrolyte changes and observed the adverse reactions.

Efficacy Determination

According to the "Stroke Patients Neurological Deficit Score", 4th National Conference of Cerebrovascular Disease, 1996, scored and determined the efficacy. almost cure: NIHSS (National Institutes of Health Stroke Scale), score reduced by 91%-100%, could resume work; significant efficacy: NIHSS score reduced by 46%-90%, could partially take care of daily living; efficacy: NIHSS score reduced by 18%-45%; without efficacy: NIHSS score reduced by 0-17%; deterioration: NIHSS score increased compared with the previous.

Statistical Analysis

SPSS16.0 software (SPSS Inc., Chiacago, IL, USA) was used for statistical analysis, measurement data were expressed with ±s, paired *t*-test for comparison of before and after treatment, *t* test for group comparison, χ^2 test for the rate comparison.

Results

Oxidative Stress Index

After the treatment, the plasma SOD and GSH-Px levels increased, while MDA levels decreased ($p < 0.01$), and the results were more significant in EG before and after the treatment, when compared with CG, the difference was statistically significance ($p < 0.01$, Table I).

NIHSS score

After the treatment, NIHSS scores of the both group all decreased ($p < 0.01$), and NIHSS score declining was more evident before and after treatment in EG than those in CG, the difference was statistically significant ($p < 0.01$, Table II).

Therapeutic Effects

In EG, the total efficiency (almost cure+significant efficacy+efficacy) was 89.1%, effective rate (almost cure+significant effecacy) was 73.9%; in CG, the total effective rate and effective rate were 70.5% and 38.6%, respectively. The total effective rates and the effective rates between the two groups had significant difference ($p < 0.01$, Table III).

Glucose and β-cell Function

Under the same insulin doses, FPG, 2HPG, HbA1c and HOMA-IR decreased and HOMA-β significantly increased after the treatment in both groups ($p < 0.05$); while the changes in EG were more significant when compared with CG ($p < 0.05$, Table IV).

Table I. Comparison of SOD, GSH-Px and MDA before and after the treatment ($\bar{x} \pm s$).

Group		Cases (n)	SOD (u/ml)	GSH-Px (enzyme energy unit)	MDA (nmol/ml)
CG	Pre-treatment	44	103.07 ± 26.85	107.50 ± 48.36	47.61 ± 23.54
	Post-treatment	44	118.46 ± 29.73*	126.31 ± 50.42*	40.84 ± 20.65*
EG	Pre-treatment	46	101.82 ± 27.21	105.89 ± 49.17	48.02 ± 24.19
	Post-treatment	46	135.49 ± 32.86$^{\varnothing,\#}$	154.10 ± 61.82$^{\varnothing,\#}$	27.63 ± 15.32$^{\varnothing,\#}$

Compared with pre-treatment, $^{*}p < 0.05$, $^{\varnothing}p < 0.01$, compared with CG, $^{\#}p < 0.01$.

Table II. NIHSS scores of two groups before and after the treatment ($\bar{x} \pm s$).

Group	Cases (n)	Pre-Tx	Post-Tx
CG	44	10.97 ± 4.62	7.29 ± 4.14*
EG	46	11.31 ± 4.38	4.05 ± 3.21*,∅

Compared with pre-treatment, *$p < 0.05$, compared with CG, ∅$p < 0.01$.

Blood Lipid

Using equal dose of lipid-lowering drug, TG, TC, LDL-C and FFA levels in two groups after treatment were significantly decreased, compared than before treatment ($p < 0.01$). There were significant differences between EG and CG ($p < 0.05$) (Table V).

Adverse Reactions

2 patients in EG had mild abdominal distension, while both remitted spontaneously within 1-2 days. Before and after the treatment, leukocytes, blood lipids, blood pressure, weight, ECG, liver and kidney function, electrolytes of all patients did not change significantly, and no patient withdrew the treatment.

Discussion

China has entered the aging society, and the prevalence of diabetes in people over 60 years old is above 20%[5]. Aged patients with T2DM are often complicated with hypertension, dyslipidemia, hyperuricemia, arteriosclerosis and other diseases, on the basis of hyperglycemia[6]. These factors can cause decreased erythrocyte deformability, en-

Table III. The effective rates of two groups.

Group	Cases (n)	AC	SE	E	WE	D	SE (%)	TE (%)
CG	44	6 (13.6)	11 (25.0)	14 (31.8)	10 (22.3)	3 (6.8)	38.6	70.5
EG	46	13 (28.6)	21 (43.5)	7 (15.2)	3 (6.5)	2 (6.5)	73.9*	89.1*

AC: almost cure; SE: significant efficacy; E: efficacy; WE: without efficacy; D: deterioration; TE: total efficacy; Compared with CG, *$p < 0.01$.

Table IV. Comparison of FPG, 2hPG, HbA1c, HOMA-IA and HOMA-β before and after the treatment ($\bar{x} \pm s$).

Group		Cases (n)	FPG (mmol/l)	2hPG (mmol/l)	HbA1c (%)	HOMA-IA	HOMA-β
CG	Pre-treatment	44	15.2 ± 3.7	20.4 ± 6.5	14.2 ± 1.9	13.78 ± 7.45	149.31 ± 62.53
	Post-treatment	44	10.4 ± 1.5*	14.8 ± 3.3*	11.7 ± 1.0*	10.84 ± 3.75*	216.25 ± 98.73*
EG	Pre-treatment	46	16.1 ± 3.6	20.7 ± 6.6	14.6 ± 2.1	13.90 ± 7.62	150.74 ± 63.28
	Post-treatment	46	7.8 ± 0.9*,∅	9.4 ± 2.1*,∅	9.2 ± 0.8*,∅	8.85 ± 3.04*,∅	286.63 ± 103.49*,∅

Compared with pre-treatment, *$p < 0.01$, compared with CG, ∅$p < 0.01$.

Table V. Comparison of TG, TC, LDL-C, FFA before and after the treatment ($\bar{x} \pm s$).

Group		Cases (n)	TG (mmol/l)	TC (mmol/l)	LDL-C (mmol/l)	FFA (mmol/l)
CG	Pre-treatment	44	3.37 ± 1.56	7.35 ± 0.91	4.64 ± 1.86	0.72 ± 0.16
	Post-treatment	44	2.25 ± 0.98*	4.86 ± 0.78*	3.05 ± 0.98*	0.42 ± 0.11*
EG	Pre-treatment	46	3.54 ± 1.61	7.58 ± 0.94	4.71 ± 1.92	0.76 ± 0.21
	Post-treatment	46	1.47 ± 0.67*,∅	3.75 ± 0.63*,∅	2.36 ± 0.75*,∅	0.34 ± 0.10*,∅

Compared with pre-treatment, *$p < 0.01$, compared with CG, ∅$p < 0.05$

hanced blood platelet viscosity, increased thromboxane B2, decreased prostacyclin level and thickened vessel wall, leading to blood viscosity increase, microcirculation disorder, and cerebral infarction[7]. The recurrence rate, morbidity and mortality of T2DM complicated with acute cerebral infarction are high, with poor prognosis[8]. Under normal condition, the brain tissue oxygen consumption accounts for about 25% of the total oxygen consumption. Brain cells contain a large amount of mitochondria, which is particularly sensitive to hypoxia. When the cerebral infarction occurs due to blood flow reduction or interruption, the mitochondria with ischemia and hypoxia mitochondria produces lots of free radicals[9]. The superfluous oxygen free radicals enter the ischemic tissue, leading to peroxidation of unsaturated fatty acids on cell membrane. So, the physiological function of cell membrane is destroyed, resulting in neuronal structural abnormalities and necrosis[10]. Therefore, prevention and treatment of damage of increased oxygen free radical and lipid peroxidation on brain cells in cerebral ischemia reperfusion stage is very important for prognosis of cerebral infarction[11].

α-lipoic acid is a powerful antioxidant. It can potently scavenge oxygen free radicals, regenerate other *in vivo* antioxidants, chelate metal ions, inhibit lipid peroxidation reaction[12]. Meanwhile, α-lipoic acid attends into the citric acid cycle, improving K^+-Na^+-ATP enzyme activity, and is the essential part in the metabolic pathway, which would produce energy. It also integrates both fat-solubility and water-solubility, could penetrate into the respective cells parts and play its roles, so it is called "universal antioxidant"[13]. α-lipoic acid has been used to treat diabetic peripheral neuropathy and diabetic nephropathy[14]. In recent years application of α-lipoic acid in central nervous system diseases has gradually attracted attention[15].

This study finds that the application of α-lipoic acid to aged T2DM complicated with acute cerebral infarction can significantly increase plasma SOD and GSH-Px levels, and decrease MDA level. This is consistent with results of Lappalainen et al's research[16]. SOD activity indirectly reflects the body's ability to eliminate oxygen free radicals. GSH-Px is an important enzyme, catalyzing the decomposition of H_2O_2 and, thus, protecting the cell membrane; MDA content as the lipid peroxidation metabolite of oxygen free radicals and biomenbrane unsaturated fatty acid, its content could reflect the attacking severity of the body by free radicals[17]. α-lipoic acid can decrease the damage from oxygen free radicals and lipid peroxidation by enhancing the activity of oxygen free radical scavenger; thus, plays a protective role for neuronal apoptosis caused by cerebral ischemia reperfusion[18]. In this study, after application of α-lipoic acid, NIHSS score is significantly decreased, while efficiency improved significantly, indicating that α-lipoic acid could prevent brain cells injury caused by the increasing oxygen free radicals and lipid peroxidation in cerebral ischemia-reperfusion period, helping to improve brain cell metabolism and promote the symptom amelioration function recovery. This is similar with the results of Vallianou et al[19].

Results of this work also show that, with the equivalent insulin dose, the application of α-lipoic acid can significantly decrease FPG, 2hPG and HbA1c, indicating a significant hypoglycemic effect, similar with Balkis et al's research[20]. After treatment, TG, TC, LDL-C and FFA significantly decreased, indicating significant lipid metabolism regulation role of α-lipoic acid. This is consistent with Butier et al's study findings[21]. Furthermore, α-lipoic acid can significantly decrease HOMA-IA level in patient, while increase HOMA-β level, indicating that α-lipoic acid can significantly lower blood sugar and blood lipid, improve islet β-cell function and reduce islet β cell damage caused by oxidative stress[22]. Throughout the whole treatment, only 2 patients have mild gastrointestinal discomfort, which is relieved spontaneously within 1-2 days. Before and after the treatment, the patients' white blood cells, blood pressure, body weight, ECG, liver and kidney function and electrolytes do not change significantly, indicating the safety of α-lipoic acid for old patients.

Conclusions

In treatment of aged T2DM complicated with acute cerebral infarction, α-lipoic acid can significantly reduce the oxidative stress level. In addition, it can lower hypoglycemic lipid, improve islet β-cell function, alleviate symptom, and promote rehabilitation, with obvious curative effect and safety. However, as the sample size in this study is relatively, small, whether the α-lipoic acid optimal dose, treatment course and curative effect are associated with patient age, still need to be further investigated.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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