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Clinical efficacy and safety of nicergoline combined with oxiracetam in the treatment of vascular cognitive impairment

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Abstract: As a α1-adrenergic receptor antagonist, nicergoline can induce vasodilation and increase arterial blood flow. Its clinical application can effectively prevent and treat cognitive impairment and reduce cognitive decline and comprehensively improve patients' daily living ability and social function. The clinical efficacy of nicergoline combined with oxiracetam in the treatment of vascular cognitive impairment after stroke was analyzed. 120 patients with cognitive impairment after stroke were randomly divided into nicergoline group and Experience group. They were treated with nicergoline and nicergoline combined with oxiracetam respectively. Both groups were treated for one month. Montreal Cognitive Assessment Scale (MoCA) was used to evaluate the cognitive function of the two groups before and after treatment, and the clinical efficacy was compared. The results showed that the average score of MoCA in the combined group was (5.97±2.06), higher than that in the nicergoline group (3.53±1.44). The change of MoCA score was the most significant. There was significant difference between the nicergoline group and the combined group ($t=4.21$, $P<0.01$). The combined group had the highest effective rate and the total effective rate was 93.3%. Conclusion: Nicergoline and oxiracetam are effective drugs in the treatment of vascular cognitive impairment (VCI). The combined use of nicergoline and oxiracetam is better than that of nicergoline alone. The combined use of nicergoline and oxiracetam can significantly improve the severity of symptoms and quality of life in patients with vascular cognitive impairment after stroke. The clinical effect is definite.

Keywords: Stroke, vascular cognitive impairment, nicergoline, oxiracetam.

INTRODUCTION

Vascular cognitive impairment (VCI), one of the common diseases in the elderly, mostly caused by cerebrovascular disease, is an important cause of senile dementia patients, which can be expressed as varying degrees of cognition, feelings, memory, personality, speech disorders (Block *et al.,* 2017). Etc., it has a great negative impact on the lives of patients and their families. The initial performance of patients with VCI may not be obvious and may be accompanied by memory loss, behavioral abnormalities, spatial and temporal disorientation, etc., but as the patient's disease develops, the clinical manifestations of patients become more and more obvious, and finally develop into dementia (Arriola *et al.,* 2018). At present, there is no specific treatment plan for VCI in the clinic, so the main purpose of VCI clinical treatment is to delay the progress of the disease and improve the quality of life of patients (Park *et al.,* 2011; Rodriguez *et al.,* 2018).

Oxiracetam is a new generation of γ-lactam drugs that improve brain function (Emir *et al.,* 2014). It can pass the blood cerebrospinal fluid barrier and activate brain cell metabolism and brain tissue protein kinase C activity, thereby inhibiting choline-induced forgetfulness (Eliane *et al.,* 2018). Niger horn is an ergot alkaloid, which has the effects of dilating cerebral blood vessels, improving cerebral circulation, increasing glucose and oxygen utilization, enhancing neurotransmitter transmission, activating dopamine D2 receptors and increasing acetylcholine concentration, thereby alleviating clinical symptoms (Zhou *et al.,* 2018). Cognitive function, quality of life and quality of life (Carmen *et al.,* 2018). Nimesil combined with oxiracetam in the treatment of vascular cognitive impairment, can quickly, safely and effectively control the patient's condition, delay its development to dementia, improve clinical treatment, improve patient's ognitive, speech and other obstacles, improve the daily living ability of patients is of great significance for improving the prognosis and outcome of patients, and it is worthy of popularization and application in clinical practice.

Stroke is a disease of cerebral blood flow disorder and brain tissue functions or structure damage caused by cerebral vascular obstruction or non-traumatic rupture (Rochin *et al.,* 2018). Stroke is a common disease of middle-aged and old people. It has a high incidence, disability and mortality, which brings heavy burden to family and society (Singh *et al.,* 2016). The disease often brings serious sequelae to patients (Shi *et al.,* 2018). Post-stroke cognitive impairment is a common complication of the disease. Some patients will have different degrees of cognitive impairment one week after the onset of the disease (Trzeciak *et al.,* 2016). The clinical manifestations are different degrees of memory, computational ability, executive ability and visual-spatial ability. Cognitive impairment can also develop to vascular dementia if it is

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not treated in time (Virginia *et al.,* 2018). Therefore, active intervention is needed for the cognitive impairment caused by stroke. In this study, patients with cognitive impairment after stroke were treated with nicergoline, nicergoline and oxiracetam. The present report is as follows.

MATERIALS AND METHODS

The enrollment cases were 120 patients with cognitive impairment after the first stroke in our department of neurology in our hospital in 2018. Criteria for selection: (1) First-episode patients who met the diagnostic criteria for stroke in China's Acute Ischemic Stroke Diagnosis and Treatment 2014, confirmed by CT or MRI; (2) Patients with varying degrees of cognitive impairment, MoCA score <26 points (3) stable vital signs clear consciousness, above primary school education, with certain reading and language communication skills; (4) age 40-80 years old; (5) agree and sign informed consent. Exclusion criteria: (1) mental retardation and coma patients; (2) mental patients; (3) patients with severe heart, liver, and renal dysfunction. 120 patients were divided into two groups according to the treatment method: Nicergolune combined with oxiracetam treatment group (Experience group) and Niger keratin group (Nimeskerin group). There was no significant difference between the two groups (P>0.05), comparable (table 1).

Inclusion criteria: (1) Complying with the diagnostic criteria of vascular cognitive impairment in the Guidelines for Diagnosis and Treatment of Vascular Cognitive Impairment; (2) Understanding the experiment and signing informed consent voluntarily; (3) There are risk factors for cerebrovascular diseases or accompanied by cerebrovascular diseases; (4) Cognitive impairment shows fluctuating progress; (5) Mild memory impairment or retention; (6) Simple essence; The Mental State Assessment Scale (MMSE) scored 24-27 points, which did not meet the dementia criteria. Exclusion criteria: (1) those with severe heart, liver and kidney dysfunction or coagulation dysfunction that cannot be corrected: (2) cognitive disorders of other causes or unknown causes; (3) those with a history of mental illness; 4) poor compliance, not cooperating with treatment.

Both groups were given routine treatment after stroke, basic treatment such as dehydration, improvement of cerebral blood supply, lipid-lowering stable plaque, nutritional nerve and so on. Nicergoline group was given Nicergoline Tablets (10mg, 3 times/day) and Experience group was treated with Nicergoline and Oxiracetam Capsules (olaine), 800mg, 3 times/day. Both groups were treated continuously for one month.

Therapeutic criteria

The Montreal Cognitive Assessment Scale (MoCA) is an assessment tool for rapid screening for mild cognitive dysfunction, including concentration, executive function, memory, language, spatial structure skills, abstract thinking, computational power and orientation. In other aspects, there are 11 items of examination, the total score is 30 points. The higher the score, the better the cognitive function, >26 is normal. A score <26 was considered to have mild cognitive dysfunction. Efficacy evaluation was performed using the MoCA scoring system and the efficacy was judged by SPSS software.

Ethical approval

All patients were approved by Ethics Committee of our hospital and signed on the informed consent. Ethical approval number as 16TTPHQS2.

STATISTICAL ANALYSIS

All the data were processed by SPSS 19.0 statistical software. Grouped t-test was used for normal test, Rank sum test was used for unsatisfactory test, Chi square test is applicable to the significance test of the rate or percentage difference between two groups and independent sample t-test was used for comparison between groups. $P < 0.05$ showed significant difference.

RESULTS

There was no significant difference in the baseline MoCA score between the two groups before treatment, but the MoCA score of the combined group was significantly higher than that of the nicergoline group after treatment ($t = 4.21$, $P<0.01$). The total effective rate of the combined group was significantly higher than that of the niergoline group ($x2=8.64$, $P<0.01$) (table 2 and 3). No serious side effects occurred in the two groups, P>0.05 (table 4).

DISCUSSION

Since Bowler put forward the concept of VCI in the 1990s, VCI has gradually attracted the attention of the medical community (Dettogni *et al.,* 2018). In recent years, with the aging of our country's population becoming more and more serious, the incidence of stroke in the elderly is also increasing. As one of the common complications of stroke, the incidence of VCI is also increasing (Kich *et al.,* 2016). At present, the purpose of clinical treatment of VCI is to control the progress of the disease and delay the development of VCI to irreversible vascular dementia. Drug therapy is the main method for clinical treatment of VCI, but the efficacy of different drugs is different. Stroke ranks third in the mortality rate of urban residents and second in the mortality rate of rural residents (Killick *et al.,* 2014).

It is one of the diseases with the highest incidence in China. About 60% of the patients had different degrees of

Table 1: MoCA Scale Score Comparison of Two Groups before and after Treatment ($\overline{\chi} \pm s$)

Group	n	Female/male	Weight (Kg)	Hemorrhagic stroke	Ischemic stroke	MoCA Scale
Nicergoline group	60	22/38	62.5±11.9	17	41	22.4±1.75
Experience group	60	19/41	66.2±13.7	20	38	25.6±1.85

Table 2: Comparison of MoCA Scale Scores before and after Treatment in Two Groups ($\overline{\chi} \pm s$)

Group	n	Before treatment	After treatment	Score changes	t value	P value
Nicergoline group	60	21.27±2.52	24.8±2.46	3.53±1.44	18.96	0.00
Experience group	60	20.75±2.56	26.72±2.53	5.97±2.06	22.455	0.00

Table 3: Comparison of Therapeutic Effects between Two Groups [n (%)]

Group	n	Basic cure	Significant progress	Progress	Unchanged	Total effective rate/%
Nicergoline group	60	2 (3.33)	18 (30.00)	24 (40.00)	16 (26.67)	7.33
Experience group	60	4 (6.67)	25 (41.67)	27 (45)	4 (6.67)	93.33$^{\#}$

Table 4: Comparison of the Incidence of Side Effects between the Two Groups

Group	Number of cases	Nausea	Drowsiness	Weak	Incidence rate
Nicergoline group	60	2	2	2	6 (10.00)
Experience group	60	2	2	2	6 (10.00)
χ^2					0.000
P					1.000

*Notes: P < 0.05 means significant difference, P < 0.01 means extremely significant difference

cognitive impairment one week after onset, and the incidence of dementia was 31.8% - 40.0% due to the further aggravation of cognitive impairment after stroke (Kim *et al.,* 2004; Kim *et al.,* 2018). Post-stroke cognitive impairment is mostly attributed to non-dementia vascular cognitive impairment (VCIND) classified by course of disease in VCI. The initiating factors are energy disorder leading to brain injury after ischemia (Lansac *et al.,* 2018). The main mechanisms are toxicity of excitatory amino acids, intracellular edema, acidosis, excessive and oxygen free radical production, cholinergic disorder, intracellular calcium overload, abnormal expression of adhesion molecules and cytokines, energy consumption and apoptotic gene stimulation (Lazarevic *et al.,* 2017). A series of cascade reactions, such as inflammatory response induced by living, ischemia/reperfusion injury, lead to a shortage of blood supply in the frontotemporal lobe of the brain (Lee *et al.,* 2017). At the same time, the interaction between neurodegenerative lesions and vascular injury after stroke exists simultaneously, which impairs the central cholinergic nervous system and the neurobiochemical basis of learning and memory in the brain. Cognitive impairment can be caused by damage to the road. Before the development of vascular dementia, early diagnosis and intervention can prevent and delay the development of VCI, and even reverse the cognitive impairment of patients (Li *et al.,* 2017).

At present, the main drugs for post-stroke cognitive impairment and vascular dementia are brain cell activator, cerebral vasodilator, cholinesterase inhibitor and non-competitive N-methyl-D-aspartate receptor antagonist. Nicergoline (ergot bromonicotinate) is an alkaloid derivative obtained in the 1970s. It has broad-spectrum effects: (1) as an adrenergic receptor antagonist, it can induce vasodilation and increase arterial blood flow; (2) improve the function of cholinergic and catecholaminergic neurotransmitters; (3) inhibit platelet aggregation; (4) Promote metabolic activities and increase the utilization of oxygen and glucose; (5) It has neurotrophic and antioxidant properties. Data show that nicergoline is associated with different causes of dementia. Its therapeutic effect has been affirmed. As high as 89% of patients have improved significantly in cognitive and behavioral aspects; most patients still have improved or stabilized after 12 months. Nicergoline improves the alertness and information processing ability of the brain and can significantly improve the severity of symptoms and quality of life. Nicergoline has been successfully used in rehabilitation treatment of patients with chronic ischemic stroke (Lin *et al.,* 2006). The adverse events of nicergoline are related to the central nervous system, metabolic system and the whole body. Most of them are considered to be typical symptoms of ergot derivatives.

Because their symptoms are generally mild and transient, treatment interruptions are relatively small (Marmitt *et al.,* 2018). The general therapeutic dose of nicergoline has good safety and tolerance and has high therapeutic value in patients with mild dementia, vascular cognitive impairment (Nordberg, 2006). Nicergoline can effectively prevent and treat cognitive impairment and reduce cognitive decline. Improving indicators include memory, attention, orientation and emotional fluctuation, and comprehensively improve patients' daily living ability and social function (Mensor *et al.,* 2001).

The chemical name of oxiracetam is 2-(4-hydroxypyrrolidine-2-keto-1-yl) -acetamide, which belongs to the analogue of piracetam, and its efficacy is 3-5 times that of piracetam (Miloso *et al.,* 2008). Oxiracetam is a pseudocholinergic brain-stimulating drug acting on the central reticular structure, which can stimulate specific central nervous pathway through blood-brain barrier, improve thinking and memory, improve academic performance and reduce memory impairment caused by shock, and antagonize the decrease of learning ability in rats with antigen-induced hypertensive cerebral vascular injury (McIlwain *et al.,* 2013). The operation of acetylcholine in rat cortex and hippocampus can increase the affinity for choline uptake, promote the synthesis of phosphatidylcholine and phosphatidy-lethanolamine, selectively activate the function of cerebral cortex and improve brain metabolism, promote the recovery of EEG after hypoxia, activate adenylate activator, promote ATP synthesis and energy storage and promote ATP adenosine triphosphate transformation, RNA synthesis and anti-platelet aggregation. Toxicological studies showed that oxiracetam had low toxicity and no mutagenicity. Oxiracetam had fewer adverse reactions and had no effect on the nervous system, cardiovascular system and respiratory system. Occasionally, anxiety, itching, rash, nausea, stomachache, etc. can be relieved after discontinuation.

Because the pathogenesis of vascular cognitive impairment is complex, there is no specific drug for the disease at present and it is difficult to achieve satisfactory therapeutic effect with a single drug (Nabavi *et al.,* 2016). Therefore, it is advocated to use combination therapy in clinic. Nicergoline is a synthetic racemate whose main active ingredient is dl-3-n-butylphthalide (Luo, 2001). The drug is a multi-target anti-cerebral ischemia drug, which can effectively improve the function of mitochondria, promote the increase of NO and PGL2 levels in cerebrovascular, and inhibit the release of glutamate and reduce its level. It can also reduce the levels of calcium ion and arachidonic acid in cells, thereby inhibiting the release of free radicals, increasing the activity of antioxidant enzymes, reducing the scope of cerebral infarction, alleviating neurological impairment, improving brain blood supply and alleviating clinical symptoms (Liu *et al.,* 2017). Relevant studies have shown that nicergoline can regulate the circulation of ischemic part to a certain extent and protect the double mechanism of mitochondria, increase the metabolic rate of brain and decrease the apoptotic rate of neurons (Mosmann, 1983). In addition, it can improve brain edema caused by ischemia. It can alleviate nerve injury, prevent platelet aggregation and reduce the possibility of thrombosis. In addition, nicergoline can improve the degeneration of hippocampal neurons and cerebral ischemic cortex by improving the level of heme oxygenase. Relevant studies have shown that nicergoline combined with oxiracetam is effective in the treatment of vascular cognitive impairment. In this study, the improvement of cognitive function and daily living ability in the study group was significantly better than that in the control group, which was consistent with the above conclusions.

CONCLUSION

From the pharmaceutical point of view, nicergoline is one of ergot alkaloids. It can alleviate VCI symptoms and improve patients' cognitive and memory functions by expanding cerebrovascular, improving cerebral circulation, strengthening neurotransmitter conduction, promoting brain metabolism and activating dopamine D2 receptor. The results showed that the MoCA scores of the two groups were significantly improved after treatment ($P < 0.01$), indicating that nicergoline, nicergoline combined with oxiracetam had a good therapeutic effect in the treatment of cognitive impairment in stroke patients, and could effectively treat cognitive impairment in stroke patients. MoCA score of combined groups was significantly better than that of nicergoline group ($P < 0.01$), indicating that the cognitive impairment of combined group was better than that of nicergoline group, indicating that nicergoline combined with oxiracetam was better than nicergoline alone in the treatment of cognitive impairment of stroke patients.

In conclusion, nicergoline combined with oxiracetam is effective in the treatment of post-stroke cognitive impairment, which can promote the early return of patients to society and is worthy of clinical application.

REFERENCES

Arriola A, Raquel FR, Xinia G and Salas G (2018). Blood concentrations of leptin and adiponectin in school children after the implementation of the model of prevention of childhood obesity "Pongale Vida", *Archi. Latin. D. Nutr.,* **68**(2): 152-163.

Block T, Petrides G and Kushner H (2017). Mifepristone plasma level and glucocorticoid receptor antagonism associated with response in patients with psychotic depression, *J. Clini. Psycho.*, **37**(5): 505.

Carmen C, Maria P and Jorge RP (2018). Development

and validation of scales to measure women's eating and satiation values: A critical factor in the treatment of obesity , *Archi. Latin. D. Nutr.,* **68**(2): 141-151.

Dettogni A, Antonio T and Marcelo M (2018). Studying the structures of in silico designed novel antimalarial drugs having lesser GlideScore, *Bolet. D. Mala. Y. Sal. Amb.,* **58**(5): 161-165.

Emir S, Sozen S, Bali I, GUrdal SO, Turan BC, Yıldırım O and Yetisyigit T (2014). Outcome analysis of laporoscopic D1 and D2 dissection in patients 70 years and older with gastric cancer. *Int. J. Clin. Exp. Med.,* **7**(10): 3501-3511.

Eliane J and Azevedo C (2018). Principle and practice of infectious disease of humans, *Bolet. D. Mala. Y. Sal. Amb.,* **58**(4): 2-7.

Kich DM, Bitencourt S, Alves C, Silva J, Pinteus S, Pedrosa R and Laufer S (2016). Neuromodulatory effects of Calyptranthes grandifolia extracts against 6-hydroxydopamine-induced neurotoxicity in SH-SY5Y cells. *Biomed. Pharm.,* **84**(5): 382-386.

Killick R, Ribe EM, Al-Shawi R, Malik B, Hooper C and Fernandes C (2014). Clusterin regulates β-amyloid toxicity via Dickkopf-1-driven induction of the wnt-PCP-JNK pathway. *Mol Psychiatry* **19**(4): 88-98.

Kim MS, Lee JI, Lee WY and Kim S (2004). Neuroprotective effect of Ginkgo biloba L. extract in a rat model of Parkinson's disease. *Phytother. Res.,* **18**(2): 663-666.

Kim HY, Jeon H, Kim H, Koo S and Kim S (2018). Sophora flavescens Aiton decreases MPP+-induced mitochondrial dysfunction in SH-SY5Y cells. *Front Aging Neurosci.,* **10**(4): 119.

Lazarevic-Pasti T, Leskovac A, Momic T, Petrovic S and Vasic V (2017). Modulators of acetyl cholinesterase activity: From Alzheimer's disease to anti-cancer drugs. *Curr. Med. Chem.,* **24**(30): 3283-3309.

Lansac F, Maria B and Oliveira F (2018). Identification and sequence analysis of Aedes aegypti mosquitoes, *Bolet. D. Mala. Y. Sal. Amb.,* **58**(6): 147-151.

Lee JK and Kim NJ (2017). Recent advances in the inhibition of p38 MAPK as a potential strategy for the treatment of Alzheimer's disease. *Molecules* **2**2(8): 1287.

Li S, Sun X, Xu L, Sun R, Ma Z, Deng X, Liu B, Fu Q and Qu R (2017). Baicalin attenuates in vivo and in vitro hyperglycemia-exacerbated ischemia/reperfusion injury by regulating mitochondrial function in a manner dependent on AMPK. *Eur. J. Pharmacol*., **815**(2): 118-126.

Lin MT and Beal MF (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature,* **443**: 787-795.

Liu Z, Zhou T, Ziegler AC, Dimitrion P and Zuo L (2017). Oxidative stress in neurodegenerative diseases: From molecular mechanisms to clinical applications. O*xid Med. Cell Longev.,* **17**(2): 2525967.

Luo Y (2001). Ginkgo biloba neuroprotection: Therapeutic implications in Alzheimer's disease. *J. Alzheimers. Dis.,* **3**(4): 401-407.

Marmitt DJ, Bitencourt S, Silva AC, Rempel C and Goettert MI (2018). Medicinal plants used in Brazil public health system with neuroprotective potential: A systematic review. *Bol. Latinoam. Caribe Plant Med. Aromat.,* **17**(2): 84-103.

McIlwain DR, Berger T and Mak TW (2013). Caspase functions in cell death and disease. *Cold Spring Harb Perspect. Biol.,* **5**(4): a008656.

Mensor FS, Menezes CC, Leitao AS, Reis TC, dos Santos CS and Coube SG (2001). Screening of Brazilian plant extracts for antioxidant activity by the use of DPPH free radical method. *Phytother. Res.,* **15**(1): 127-130.

Miloso M, Scuter A, Foudah D and Tredici G (2008). MAPKs as mediators of cell fate determination: An approach to neurodegenerative diseases. *Curr. Med. Chem.,* **15**(6): 538-548.

Mosmann T (1983). Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. *J. Immunol. Methods,* **65**(1-2): 55-63.

Nabavi SF, Braidy N, Orhan IE and Nabavi SM (2016). Rhodiola rosea L. and Alzheimer's disease: From farm to pharmacy. *Phytother. Res.,* **30**(4): 30-36.

Nordberg A (2006). Mechanisms behind the neuroprotective actions of cholinesterase inhibitors in Alzheimer disease. *Alzheimer Dis. Assoc. Disord.,* **20**(2 Suppl 1): S12-S18.

Park KR, Nam D, Yun HM, Lee SG, Jang HJ, Sethi G, Cho SK and Ahn KS (2011). β-Caryophyllene oxide inhibits growth and induces apoptosis through the suppression of PI3K/AKT/mTOR/S6K1 pathways and ROS-mediated MAPKs activation. *Cancer Lett.,* **312**(1): 178-188.

Rodriguez R, Armando C and Maribel RL (2018). Relationship between body composition and blood leptin concentration in female college students. *Archi. Latin. D. Nutr.,* **68**(2): 175-183.

Rochin M, Jesus J, Ramirez K and Rangel P (2018). Increase in nutritional value, antioxidant activity and inhibitory potential of alpha-glucoside in brownies from cooked legumes, *Archi. Latin. D. Nutr.,* **68**(2): 164-174.

Shi Y and Zhu Q (2018). Detection of Methylene tetra hydrofolate Reductase Gene C677T Mutation by PCR-RFLP, *Bolet. D. Mala. Y. Sal. Amb.,* **58**(6): 152-158.

Singh DP, Singh SS, Singh S, Shrivastava AK, Sinha K. (2016). Clinical profile of acute coronary syndrome (ACS) in young adults of North Indian population. *J. Assoc. Physicians India*, **64**(1): 33.

Trzeciak P and Wozakowska-Kapłon B (2016). Comparison of Inhospital and 12- and 36-Month Outcomes After Acute Coronary Syndrome in Men Versus Women <40 Years (from the PL-ACS Registry). *Am. J. Cardiol*., **118**(9): 1300-1305.

Virginia MA, Laura V and Hernandez-Madrigal J (2018).

Physical and nutritional characterization of tuber meal of "Malanga" (Colocasia esculenta L. Schott) of Actopan, Veracruz, Mexico, *Archi. Latin. D. Nutr.,* **68**(2): 175-183.

Zhou Y, Lv C and Wang Y (2018). Emergency Nursing Intervention Procedure for Cerebral Infarction Thrombolysis Patients with Neurological Defects, *Bolet. D. Mala. Y. Sal. Amb.,* **58**(5): 148-153.