EFFECT OF GANGLIOSIDE COMBINED WITH PRAMEXOL IN THE TREATMENT OF PARKINSON'S DISEASE AND ITS EFFECT ON MOTOR FUNCTION

EFEKAT GANGLIOZIDA U KOMBINACIJI SA PRAMEKSOLOM U LEČENJU PARKINSONOVE BOLESTI I NJEGOV UTICAJ NA MOTORIČKU FUNKCIJU

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Summary

Background: This study was aimed to evaluate the efficacy of pramipexole combined with ganglioside for PD treatment and pramipexole monotherapy, so as to provide reference for clinical practice.

Methods: 61 PD patients selected from June 2019 to December 2020 at our hospital were divided into two groups. The control group (n=31) was given dopaside oral treatment, and the treatment group (n=30) was given ganglioside combined with pramipexole. The clinical efficacy, adverse reactions, motor function scores, UPDRS scores, PDQ-39 scale scores, TNF-α levels, and related serum factor levels were measured in this study.

Results: Compared with control group, the total effective rate was obviously increased. The CRP and TNF-α levels, the speech tone and speed, sitting and walking posture, writing and hands ability scores were reduced, while the BDNF level was increased in treatment group. During the period, compared with the control group, the incidence of adverse reactions in the treatment group was significantly decreased.

Conclusion: Ganglioside combined with pramipexole were effective in treating PD. It can effectively reduce the levels

Kratak sadržaj

Uvod: Ova studija je imala za cilj da proceni efikasnost pramipeksola u kombinaciji sa gangliozidom za lečenje PD i monoterapiju pramipeksolom, kako bi se pružila referenca za kliničku praksu.

Metode: 61 pacijent sa PB odabran od juna 2019. do decembra 2020. u našoj bolnici podeljen je u dve grupe. Kontrolnoj grupi (n=31) je davan oralni tretman dopasizidom, a grupi za lečenje (n=30) davan je gangliozid u kombinaciji sa pramipeksolom. U ovoj studiji su mereni klinička efikasnost, neželjene reakcije, rezultati motoričke funkcije, UPDRS rezultati, rezultati na skali PDK-39, nivoi TNF-α i povezani nivoi faktora u serumu.

Rezultati: U poređenju sa kontrolnom grupom, ukupna efektivna stopa je očigledno povećana. Nivoi CRP i TNF-α, ton i brzina govora, položaj sedenja i hodanja, rezultati pisanja i sposobnosti ruku su smanjeni, dok je nivo BDNF povećan u grupi na lečenju. Tokom perioda, u poređenju sa kontrolnom grupom, incidencija neželjenih reakcija u grupi koja je lečena je značajno smanjena.

Zaključak: Gangliozid u kombinaciji sa pramipeksolom bio je efikasan u lečenju PD. Može efikasno smanjiti nivoe CRP i TNF-α, povećati nivo BDNF, poboljšati neurološku funkciju,

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of CRP and TNF-α, increase the level of BDNF, improve neurological function, improve motor function, and does not increase the adverse reactions of patients. It is worthy of application.

Keywords: PD, Gangliosides, Pramipexole, Motor function, UPDRS

poboljšati motoričku funkciju i ne povećava neželjene reakcije pacijenata. Dostojan je primene.

Ključne reči: PD, gangliosides, pramipeksol, motorna funkcija, UPDRS

Introduction

Parkinson's disease (PD), also known as paralysis of tremor, is a degenerative neurological disease commonly seen in the middle-aged and elderly (1), clinically characterized by static tremor, motor retardation, myotonia, and postural balance disorders. If treatment is not timely, patients may lose the ability to care for themselves (2). The incidence of PD is 1%-2% in people in their 60s (3), but increases to 3%–4% in people in their 80s (4). The prevalence of PD in China ranges from 16 to 440.3 per 100,000, and the annual incidence ranges from 1.5 to 8.7 per 100,000. The quality of life (QOL) of patients with PD is severely reduced, and they lack the ability to take care of themselves, which brings a heavy burden to their families (5). Currently, drug treatment programs for PD shows a degree of efficacy. Therefore, choosing an appropriate treatment plan is essential for relieving symptoms and improving the patients' quality life.

Levodopa has been reported to become the most effective drug for the treatment of PD. However, it has now been confirmed that most patients receiving levodopa treatment in the early stage of PD, especially those with high doses, will have motor complications. Pramipexole is a non-ergot alkaloid dopamine receptor agonist with high selectivity for the D2 subfamily of dopamine receptors and a preferential affinity for D3 receptors (6). It is used in the single and adjuvant therapy of PD and has been approved in the USA for the treatment of early and late PD (7, 8). Pramipexole delays motor complications caused by levodopa in the early stage of PD through a neuroprotective effect (9, 10), controls motor symptoms and alleviates depression in PD patients (11, 12). Ganglioside, one of the major cerebral gangliosides, is a sphingolipid composed of three structural units (13). This molecule has been regarded as an important regulator of various brain functions because of its regulation of neuronal plasticity, neuronutrient release, neurotransmission, and its interaction with neuroregulatory proteins (14). In addition, exogenous gangliosides have been shown to affect the survival of dopaminergic neurons, glutamate neurons and cholinergic neurons (15). The therapeutic effect of GM1 ganglioside has been demonstrated in PD patients (16, 17) and MPTP-treated mice (18, 19), showing neuroprotective or neurorepair effects (20).

Although the efficacy of pramipexole alone in PD treatment has been extensively studied, the effect of pramipexole and ganglioside combination therapy on inflammatory cytokines and on patients' motor function has not been reported. Therefore, this study was aimed to evaluate the efficacy of pramipexole combined with gangliosides for PD treatment and pramipexole monotherapy, so as to provide reference for clinical practice.

Materials and Methods

Research object

Total of 61 PD patients were selected from June 2019 to December 2020 at above hospital, and divided into control group (n=31) and treatment group (n=30). Inclusion criteria: According to the diagnostic criteria in the Chinese Parkinson's Disease Treatment Guidelines (Second Edition), patients aged 50–80 years old, with an education level of elementary school or above, and who meet the diagnostic criteria for PD were collected. Exclusion criteria: Psychiatric patients; patients with poor treatment compliance; patients with heart, liver, and kidney dysfunction; patients with secondary Parkinson's syndrome caused by poisoning, trauma, etc.; patients with oral uric acid-lowering drugs, patients with a history of gout or hyperuricemia; those with obvious allergies or adverse reactions to the drugs in this study; those with incomplete data. All patients have signed informed consent and this study was approved by the ethics committee of this hospital (Approval no. 20190436).

Treatment methods

(1) The control group was given dopasserzide tablets (Shanghai Fuda Pharmaceutical Co., Ltd., National Medicine Zhunzi H20143411, 0.125 g/tablet, Shanghai, China) treatment, the initial dose was 0.125 g/time, 3 times/d, according to the patient's specific conditions. The dosage can be adjusted reasonably for the condition of the disease, and the dosage can be adjusted every 2 weeks, and the maximum dosage should not exceed 0.25 g/time.

(2) The treatment group was given ganglioside combined with pramipexole: monosialotetrahexose ganglioside sodium injection (Harbin Medical University Pharmaceutical Co., Ltd., National Medicine Standard H20064601, 2 mL: 20 mg) 40 mg dissolved in 250 mL 0.9% sodium chloride injection for

intravenous drip, 2 times a day; oral pramipexole hydrochloride tablets (Boehringer Ingelheim Pharmaceutical Co., Ltd., Germany, National Medicine Standard H20140917, 0.25 mg/tablet) 0.25 g/time, 3 times/d. Both groups of patients took 2 weeks as a course of treatment. The drug was stopped for 10 days after 1 course of treatment, and then the next course of treatment was continued for 3 months. During treatment, the patient's condition was monitored, and the treatment was stop in time and make corresponding adjustments in case of abnormalities.

Evaluation Criteria

(1) UPDRS reduction rate was applied to evaluate the clinical efficacy after treatment for 4, 8, and 12 weeks (21): including mental, behavioral and emotional, activities of daily living and motor symptoms. The higher the score, the more severe the illness.

(2) The PDQ-39 was applied to evaluate the QOL before and after treatment, including daily living activities, cognition, activities, communication, and social support. The higher the scores, the lower the QOL (22).

(3) Parkinson's motor function score was applied to assess the motor function of the two groups after treatment for 12 weeks. It was divided into three aspects: speech intonation and speed, sitting and walking posture, writing and hands-on ability. The higher the scores, the worse the motor function.

(4) Measurement of the treatment effects: markedly effective means that the clinical symptoms disappear and vital signs return to normal, and the UPDRS score reduction rate is 30%; effective is the improvement of clinical symptoms and vital signs, 5% UPDRS score reduction rate is less than 30%; invalid is did not meet the above standards.

(5) Measurement of the incidence of adverse reactions, including insomnia, dizziness, nausea, and vomiting.

Observation indicators

5 mL of venous blood was collected from the patient in the morning on an empty stomach, and then froze in 80 °C refrigerator. ELISA kit was used to determine the serum TNF-α, serum CRP and BDNF levels, and an automatic biochemical analyzer was applied for measuring serum cystatin C.

Statistical analysis

The data obtained was analyzed by Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, NY, USA). The measurement data were ex-

pressed as ($\bar{x}\pm s$) and the count data were tested by chi-square test. After the normality test, the t-test was used for those with normal distribution and the variance was uniform, the t-test was used for the non-uniform variances, and the non-parametric test was used for the non-normal distribution. $P < 0.05$ was considered as statistical difference.

## Results

Measurement of baseline data

Treatment group: 30 males and 17 females; age 46–73 years, average age (59.83±4.15) years; course of disease 1–8 years, average course of disease (4.13±0.45) years; according to Hoehn-Yahr classification: grade I (6 cases), grade II (8 cases), and grade III (16 cases). Control group: 43–74 years old, average age (58.96±4.76) years; disease course 1–7 years, average disease course (3.97±0.71) years; According to Hoehn-Yahr classification: grade I (7 cases), grade II (9 cases), and grade III (15 cases). The two groups of general data are comparable (P>0.05) (*Table I*, *Table II*), indicating that the two groups of subjects had good consistency and comparability when they were enrolled in the group.

Table I General characteristics of the two group.

Feature	Control	Treatment
Age		
<60	18(58.1)	18(60.0)
≥60	13(41.9)	12(40.0)
Average age	59.83±4.15	58.96±4.76
Gender		
Male	21(67.7)	22(73.3)
Female	10(32.3)	8(26.7)
Exercise habits		
Yes	8(25.8)	10(33.3)
No	23(74.2)	20(66.7)
Weight		
<55	11(35.5)	9(30.0)
≥55	20(64.5)	21(70.0)
Course of disease	4.13±0.45	3.97±0.71

Table II Hoehn-Yahr classification of the two groups.

Group	Grade I	Grade II	Grade III
Control group	7(22.6)	9(29.0)	15(48.4)
Treatment group	6(20.0)	8(26.7)	16(53.3)
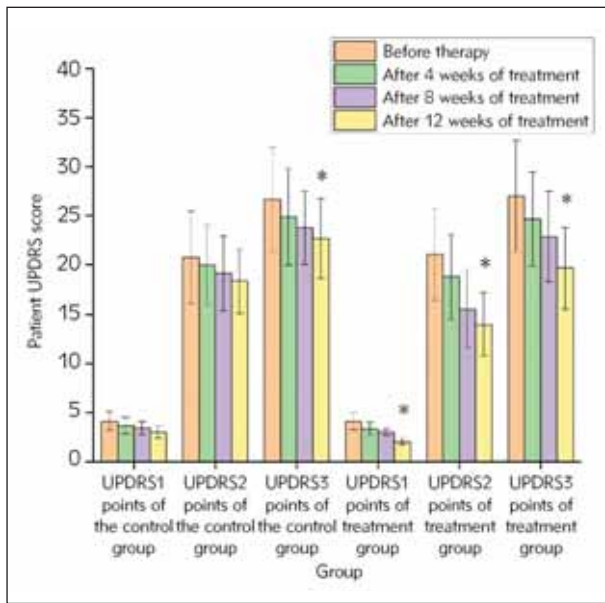
Figure 1 Measurement of UPDRS scores of patients after treatment. *P<0.05 vs before treatment

Measurement of UPDRS score changes

The difference of UPDRS1, UPDRS2, and UPDRS3 scores of the two groups was not statistically significant before treatment. After treatment for 4, 8, 12 weeks, the UPDRS scores were obviously decreased in the two group, and the UPDRS scores in the treatment group were reduced markedly in comparison with control group after treatment for 12 weeks, as shown in *Figure 1*, suggesting gangliosides combined with pramipexole and dopasazine tablets can better improve the patient's motor function, balance ability and daily activity ability.

Table III Measurement of PDQ-39 scores after treatment.

Group	Before treatment	After treatment
Control group	48.32±6.73	41.64±4.68*
Treatment group	49.13±6.82	37.23±4.03*#

*P<0.05 vs. the control group; #P<0.05 vs. before treatment

Measurement of PDQ-39 scale points

The PDQ-39 scores of patients in the two group did not change significantly before treatment. After 12 weeks of treatment, the PDQ-39 scores of the treatment group were significantly reduced in comparison with control group, as shown in *Table III*.

Parkinson's motor function score

After treatment, the scores of speech, tone and speed, sitting and walking posture, writing and hand ability in the two groups were reduced. The motor function score in the treatment group was markedly reduced versus to control group, indicating that the degree of improvement of the motor function was better after treatment (*Table IV*).

Measurement of treatment effects

The total effective rate in the treatment group was elevated obviously versus to control group after treatment for 4, 8 and 12 weeks, as shown in *Figure 2*.
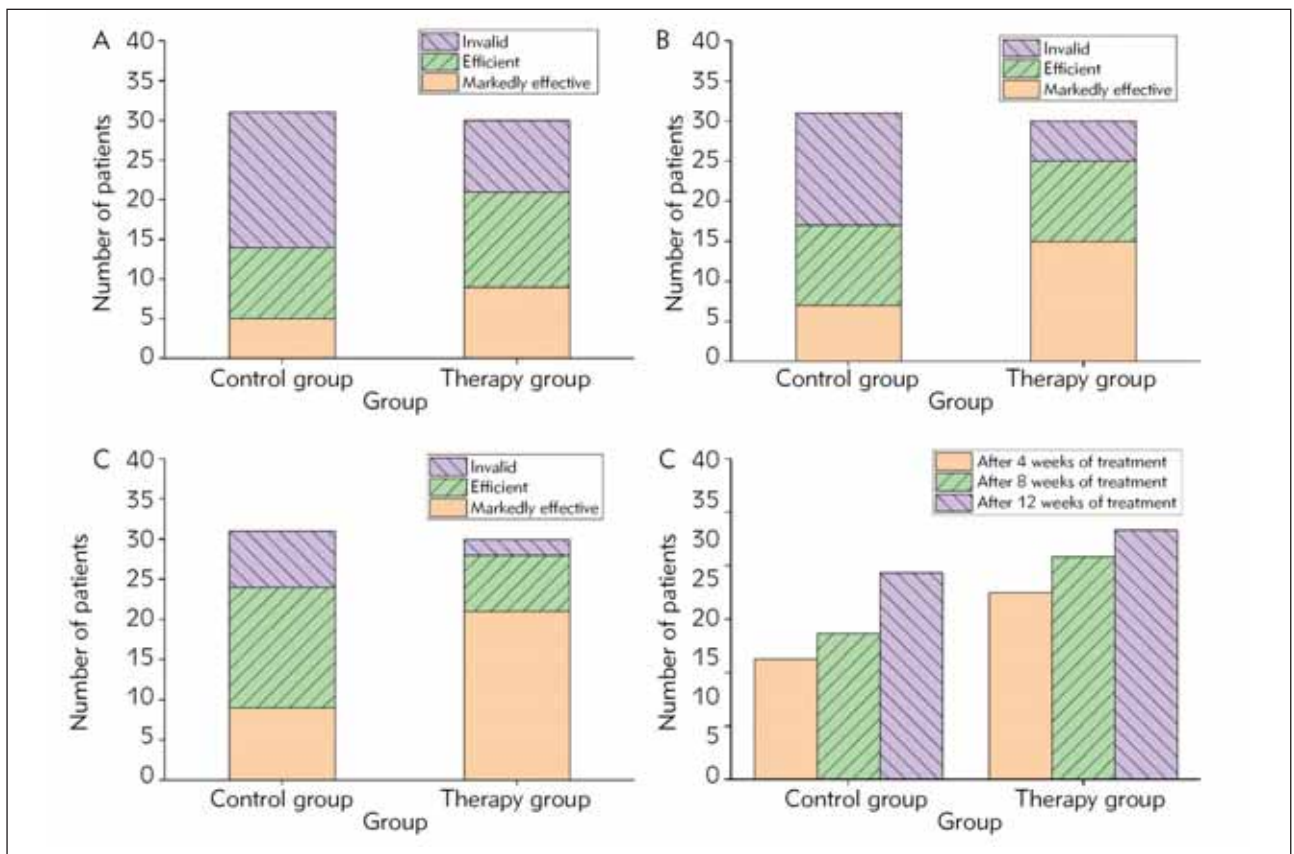
Measurement of adverse reactions

After treatment, the incidence of vomiting, depression and anorexia in the treatment group were obviously decreased. After targeted treatment, the patients recovered well without causing more serious consequences. The incidence of palpitations, nausea, and diarrhea in the treatment group was reduced, but there was no statistical difference, as shown in *Table V*.

Measurement of TNF-α levels after treatment

The serum TNF-α levels of the two groups before treatment were $(4.87\pm0.41) \times 10^{-3}$ mg/L and $(4.94\pm0.50) \times 10^{-3}$ mg/L, respectively, and there was no significant difference, indicating that they were comparable. The TNF-α level continued to decrease with the increase in the course of treatment.

Table IV Measurement of motor function scores.

Time	Group	Speech intonation and speed	Sitting and walking posture	Writing and hands-on skills
Before treatment	Control group	11.17±2.45	8.71±2.12	4.47±1.05
	Treatment group	11.32±2.03	8.67±1.84	4.52±1.19
After treatment	Control group	8.97±1.41*	6.45±1.56*	2.74±0.41*
	Treatment group	6.03±1.25*#	4.23±1.47*#	1.11±0.39*#

*P<0.05 vs. the control group; #P<0.05 vs. before treatment

Figure 2 Comparison of treatment effects after treatment. (A) Comparison of clinical efficacy at 4 weeks after treatment, (B) Comparison of clinical efficacy at 8 weeks after treatment, (C) Comparison of clinical efficacy at 12 weeks after treatment, (D) Comparison of total effective rate after treatment.

**Table V** Proportion of adverse reactions.

Adverse reactions	Control group (n=31)	Treatment group (n=30)
Anorexia	6 (19.4)	3 (10.0)
Headache	4 (12.9)	1 (3.3)
Vomit	3 (9.7)	2 (6.7)
Nausea	3 (9.7)	2 (6.7)
Listless	3 (9.7)	1 (3.3)
Diarrhea	4 (12.9)	2 (6.7)
Liver damage	2 (6.4)	1 (3.3)
Kidney damage	3 (9.7)	2 (6.7)
Total incidence of adverse reactions	17 (54.8)	10 (33.3)*

*$P<0.05$ vs. the control group.

The treatment group was treated after 8 weeks, there was a statistical difference compared with before treatment. After 12 treatment, both groups were significantly reduced (*Figure 3*). Importantly, the TNF-α level in the treatment group was obviously down-regulated, relative to control group.

Measurement of related serum factors

In the treatment group, the serum BDNF was $(11.23\pm2.44) \times10^{-3}$ mg/L, CRP was $(5.98\pm1.71) \times10^{3}$ mg/L, and Cystatin C was $(1.08\pm0.32) \times10^{3}$ mg/L; the control group was $(11.41\pm2.32) \times10^{-3}$ mg/L, $(5.96\pm1.66) \times10^{3}$ mg/L, $(1.08\pm0.27) \times10^{3}$ mg/L, respectively, and there was no significant difference, and they were comparable before treatment. After treatment for 4 weeks, the control group's serum BDNF was $(12.53\pm2.42) \times10^{-3}$ mg/L, CRP was $(5.41\pm1.44) \times10^{3}$ mg/L, and Cystatin C was $(1.08\pm0.24) \times10^{3}$ mg/L, the treatment group was $(14.22) \pm2.77) \times10^{-3}$ mg/L, $(4.98\pm1.47) \times10^{3}$ mg/L, $(1.04\pm0.27) \times10^{3}$ mg/L. After treatment for 8 weeks, the treatment group' serum BDNF was $(16.03\pm3.10) \times10^{-3}$ mg/L, CRP was $(4.10\pm1.22) \times10^{3}$ mg/L, and Cystatin C was $(1.01\pm0.15) \times10^{3}$ mg/L; the control group was $(13.97\pm2.) \times10^{-3}$ mg/L, $(5.03\pm1.21) \times10^{3}$ mg/L, $(1.07\pm0.18) \times10^{3}$ mg/L, respectively. After treatment for 12 weeks, the treatment group' serum BDNF was $(18.55\pm3.47) \times10^{-3}$ mg/L, CRP was $(3.47\pm1.04) \times10^{3}$ mg/L, and Cystatin C was $(0.97\pm0.11) \times10^{3}$ mg/L, the control group was $(14.79) \pm2.93) \times10^{-3}$ mg/L, $(4.59\pm1.17) \times10^{3}$ mg/L, $(1.06\pm0.16) \times10^{3}$ mg/L, there was statistically significant difference, as shown in *Table VI*.
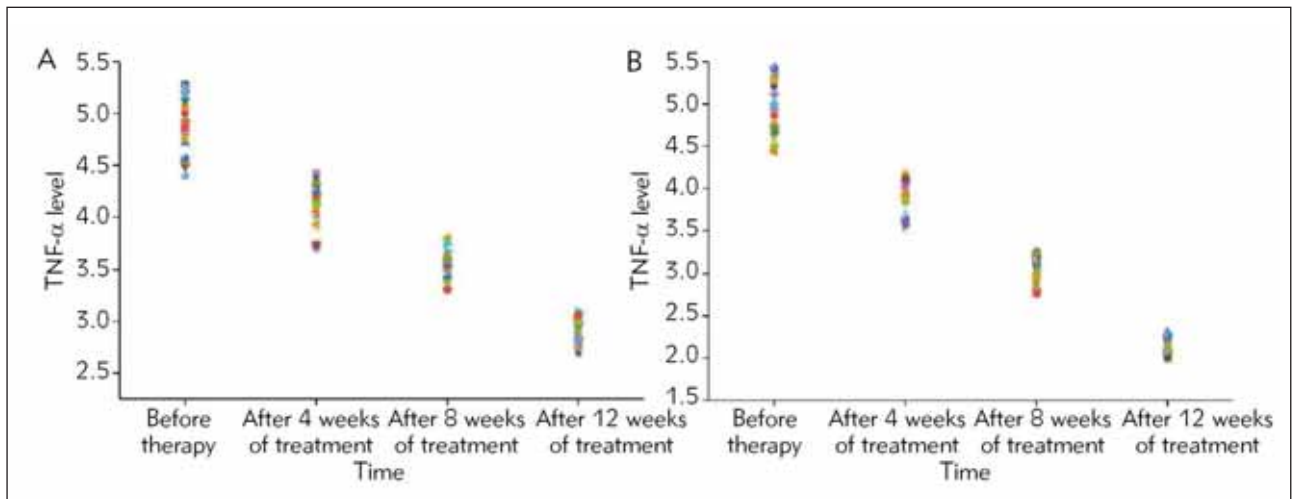
Figure 3 (A) Measurement of serum TNF-α levels after treatment in Control group and (B) Treatment group.

Table VI Measurement of serum BDNF, serum cystatin C and serum CRP levels after treatment.

Group		Before treatment	After 4 weeks of treatment	After 8 weeks of treatment	After 12 weeks of treatment
Control group	BDNF ($\times 10^{-3}$ mg/L)	11.41±2.32	12.53±2.42	13.97±2.75	14.79±2.93#
	CRP ($\times 10^3$ mg/L)	5.96±1.66	5.41±1.44	5.03±1.21	4.59±1.17#
	Cystatin C ($\times 10^3$ mg/L)	1.08±0.27	1.08±0.24	1.07±0.18	1.06±0.16
Treatment group	BDNF ($\times 10^{-3}$ mg/L)	11.23±2.44	14.22±2.77	16.03±3.10*	18.55±3.47*#
	CRP ($\times 10^3$ mg/L)	5.98±1.71	4.98±1.47	4.10±1.22*	3.47±1.04*#
	Cystatin C ($\times 10^3$ mg/L)	1.08±0.32	1.04±0.27	1.01±0.15	0.97±0.11

*$P<0.05$ vs. control group; #$P<0.05$ vs. before treatment

Discussion

Clinically, dopasizide tablets are the first choice as a treatment drug for PD patients, which can effectively improve the symptoms of PD patients. However, after 3 to 5 years of use of the drug, its efficacy gradually diminished, and it also increased adverse drug reactions (23). Pramipexole, a dopamine receptor agonist, relieves the motor symptoms of PD patients. It has obvious advantages in improving depression in patients (24), which can be activated by Dopamine receptors in the substantia nigra and striatum of the midbrain maintain the normal discharge of striatal neurons (25), and can also protect dopamine cells and reduce nerve cell damage or death (26–28). Therefore, the combination of pramipexole and dopaserizide can not only reduce the dose of dopaserizide, but also significantly improve the motor function of PD patients.

Dopaserizide is a compound preparation composed of benserazide and levodopa, which has a decarboxylation effect. As an intermediate in the biosynthesis of dopa gum, levodopa can effectively treat tremor paralysis and relieve PD patients' symptoms. However, with the prolongation of treatment time, dopasrazide is likely to cause »end-of-dose phenomenon«, and a single drug cannot achieve the best effect. However, clinical trials have proved that the new dopamine receptor agonist pramipexole hydrochloride tablets have a significant effect on the motor symptoms and non-motor symptoms of Parkinson's (29). This study displayed that PD patients treatment with pramipexole combined with ganglioside showed a significant increase in UPDRS1, UPDRS2, UPDRS3 and PDQ-39 scores. Importantly, the incidence of adverse reactions of treatment group was reduced remarkably, indicating that pramipexole combined

with ganglioside was more effective than dopasserzid alone in relieving symptoms and improving QOL in PD patients.

TNF-α has been shown to relieve depression' symptoms. Although the pathogenesis of PD has not been uncovered, the environment and genetics may play very important roles in the cause of PD. During the study of PD, researchers found that the serum TNF-α level of PD patients was increased, which was also closely related to PD' severity, indicating TNF-α as a potential biomarker for PD prognosis (30). In this study, the serum TNF-α levels were significantly reduced after treatment, and the TNF-α level in the treatment group was obviously elevated relative to control group.

BDNF is a polypeptide hormone whose role is to repair damaged neurons, so the decline of BDNF is a signal of the occurrence of cognitive dysfunction (31), which shows that the level of BDNF can show the degree of cognitive dysfunction in patients. Studies have shown that serum cystatin C, as a cathepsin inhibitor, is closely related to many neurological diseases (32). In this treatment, serum Cystatin C and CRP were significantly reduced, and in the statistics of the above two groups of data, the treatment group was decreased more significantly than the control group, and the BDNF was increased significantly, relative to the control group, which showing that pramipexole plays a very good role in regulating the serum content of PD. The possible reason is that the treatment group was given pramipexole combined with ganglioside treatment. Ganglioside has a strong antioxidant effect, which can effectively remove oxygen free radicals, reduce the level of malondialdehyde in the patient's body, and increase the body's anti-oxidant effect. The level of oxidase, which in turn achieves the effect of inhibiting the level of oxidative stress in the body (33), protects neurons and avoids free radicals from persecuting them. At the same time, gangliosides can increase the level of brain-derived neurotrophic factor, and it can effectively repair damaged neurons, thereby improving patients' cognitive level (34).

The findings of this study demonstrate that the combination of pramipexole and ganglioside treatment for patients with Parkinson's disease significantly improves clinical symptoms compared to the dopasrazide treatment group. This combination therapy can greatly reduce the occurrence of adverse reactions, improve motor function, and enhance patients' quality of life. Pramipexole has a long half-life and can be rapidly absorbed after oral administration, allowing for sustained stimulation of the postsynaptic membrane and optimal therapeutic efficacy. Additionally, the synergistic effect of combining ganglioside with pramipexole can promote patient recovery while reducing the required dosage of drugs. This results in a lower incidence of adverse reactions, making the combination therapy a safer option for clinical application.

In summary, the combination of ganglioside and pramipexole has an ideal effect for PD treatment. It can effectively improve the patient's condition, increase the level of BDNF, reduce the index level of cystatin C and CRP, and help eliminate the adverse effects of previous drugs. The clinical effect is obvious and it is worthy of promotion.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

References

1. Zhao H, Ning Y, Cooper J, Refoios CR, Ni X, Yi B, et al. Indirect Comparison of Ropinirole and Pramipexole as Levodopa Adjunctive Therapy in Advanced Parkinson's Disease: A Systematic Review and Network Meta-Analysis. Adv Ther 2019; 36(6): 1252–65.

2. Postuma RB, Gagnon JF, Bertrand JA, Genier MD, Montplaisir JY. Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials. Neurology 2015; 84(11): 1104–13.

3. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers 2017; 3: 17013.

4. Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis. Neuroepidemiology 2016; 46(4): 292–300.

5. Zhao H, Ning Y, Cooper J, Refoios CR, Ni X, Yi B, et al. Indirect Comparison of Ropinirole and Pramipexole as Levodopa Adjunctive Therapy in Advanced Parkinson's Disease: A Systematic Review and Network Meta-Analysis. Adv Ther 2019; 36(6): 1252–65.

6. Zhou H, Li S, Yu H, Sun S, Wan X, Zhu X, et al. Efficacy and Safety of Pramipexole Sustained Release versus Immediate Release Formulation for Nocturnal Symptoms in Chinese Patients with Advanced Parkinson's Disease: A Pilot Study. Parkinsons Dis-Us 2021; 2021: 8834950.

7. Wang Y, Sun SG, Zhu SQ, Liu CF, Liu YM, Di Q, et al. Analysis of pramipexole dose-response relationships in Parkinson's disease. Drug Des Devel Ther 2017; 11: 83–9.

8. Utsumi H, Okuma Y, Kano O, Suzuki Y, Iijima M, Tomimitsu H, et al. Evaluation of the efficacy of pramipexole for treating levodopa-induced dyskinesia in patients with Parkinson's disease. Internal Med 2013; 52(3): 325–32.

9. Jiang DQ, Jiang LL, Wang Y, Li MX. The role of prami-pexole in the treatment of patients with depression and Parkinson's disease: A meta-analysis of randomized controlled trials. Asian J Psychiatr 2021; 61: 102691.

10. Antonini A, Barone P, Ceravolo R, Fabbrini G, Tinazzi M, Abbruzzese G. Role of pramipexole in the management of Parkinson's disease. Cns Drugs 2010; 24(10): 829–41.

11. Smith JA, Das A, Ray SK, Banik NL. Role of pro-inflammatory cytokines released from microglia in neurodegenerative diseases. Brain Res Bull 2012; 87(1): 10–20.

12. Wang Q, Liu Y, Zhou J. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. Transl Neurodegener 2015; 4: 19.

13. Guo YL, Duan WJ, Lu DH, Ma XH, Li XX, Li Z, et al. Autophagy-dependent removal of alpha-synuclein: a novel mechanism of GM1 ganglioside neuroprotection against Parkinson's disease. Acta Pharmacol Sin 2021; 42(4): 518–28.

14. Sipione S, Monyror J, Galleguillos D, Steinberg N, Kadam V. Gangliosides in the Brain: Physiology, Pathophysiology and Therapeutic Applications. Front Neurosci-Switz 2020; 14: 572965.

15. Schneider JS, Cambi F, Gollomp SM, Kuwabara H, Brasic JR, Leiby B, et al. GM1 ganglioside in Parkinson's disease: Pilot study of effects on dopamine transporter binding. J Neurol Sci 2015; 356(1–2): 118–23.

16. Yahi N, Di Scala C, Chahinian H, Fantini J. Innovative treatment targeting gangliosides aimed at blocking the formation of neurotoxic alpha-synuclein oligomers in Parkinson's disease. Glycoconjugate J 2022; 39(1): 1–11.

17. Itokazu Y, Fuchigami T, Morgan JC, et al. Intranasal infusion of GD3 and GM1 gangliosides downregulates alpha-synuclein and controls tyrosine hydroxylase gene in a PD model mouse. Mol Ther 2021; 29(10): 3059–71.

18. Schneider JS, Aras R, Williams CK, Koprich JB, Brotchie JM, Singh V. GM1 Ganglioside Modifies alpha-Synuclein Toxicity and is Neuroprotective in a Rat alpha-Synuclein Model of Parkinson's Disease. Sci Rep-Uk 2019; 9(1): 8362.

19. Wu G, Lu ZH, Seo JH, Alselehdar SK, DeFrees S, Ledeen RW. Mice deficient in GM1 manifest both motor and non-motor symptoms of Parkinson's disease; successful treatment with synthetic GM1 ganglioside. Exp Neurol 2020; 329: 113284.

20. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Movement Disord 2008; 23(15): 2129–70.

21. Katsarou Z, Bostantjopoulou S, Peto V, Alevriadou A, Kiosseoglou G. Quality of life in Parkinson's disease: Greek translation and validation of the Parkinson's disease questionnaire (PDQ-39). Qual Life Res 2001; 10(2): 159–63.

22. Jiang DQ, Zang QM, Jiang LL, Wang Y, Li MX, Qiao JY. Comparison of pramipexole and levodopa/benserazide combination therapy versus levodopa/benserazide monotherapy in the treatment of Parkinson's disease: a systematic review and meta-analysis. N-S Arch Pharmacol 2021; 394(9): 1893–905.

23. Pagano G, Niccolini F, Wilson H, Yousaf T, Khan NL, Martino D, et al. Comparison of phosphodiesterase 10A and dopamine transporter levels as markers of disease burden in early Parkinson's disease. Movement Disord 2019; 34(10): 1505–15.

24. Deleidi M, Gasser T. The role of inflammation in sporadic and familial Parkinson's disease. Cell Mol Life Sci 2013; 70(22): 4259–73.

25. Muller SK, Bender A, Laub C, Hogen T, Schlaudraff F, Liss B, et al. Lewy body pathology is associated with mitochondrial DNA damage in Parkinson's disease. Neurobiol Aging 2013; 34(9): 2231–3.

26. Mcgeer PL, Itagaki S, Boyes BE, et al. Reactive microglia are positive for HLA-DR in the substantion nigra of Parkinson's and Alzheimer's disease brains. Neurology 1988; 38(8): 1285–91.

27. Tyagi RK, Bisht R, Pant J, Kumar P, Majeed AB, Prakash A. Possible role of GABA-B receptor modulation in MPTP induced Parkinson's disease in rats. Exp Toxicol Pathol 2015; 67(2): 211–7.

28. Pinter MM, Pogarell O, Oertel WH. Efficacy, safety, and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: a double blind, placebo controlled, randomised, multicentre study. J Neurol Neurosur Ps 1999; 66(4): 436–41.

29. Farbood Y, Sarkaki A, Dolatshahi M, Taqhi MS, Khodadadi A. Ellagic Acid Protects the Brain Against 6-Hydroxydopamine Induced Neuroinflammation in a Rat Model of Parkinson's Disease. Basic Clin Neurosci 2015; 6(2): 83–9.

30. Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacol Biochem Behav 1997; 56(1): 131–7.

31. Kottgen A, Selvin E, Stevens LA, Levey AS, Van Lente F, Coresh J. Serum cystatin C in the United States: the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis 2008; 51(3): 385–94.

32. Schapira AH, Jenner P. Etiology and pathogenesis of Parkinson's disease. Movement Disord 2011; 26(6): 1049–55.

33. Oster S, Radad K, Scheller D, Hesse M, Balanzew W, Reichmann H, et al. Rotigotine protects against glutamate toxicity in primary dopaminergic cell culture. Eur J Pharmacol 2014; 724: 31–42.

34. Koutsilieri E, Riederer P. Excitotoxicity and new antiglutamatergic strategies in Parkinson's disease and Alzheimer's disease. Parkinsonism Relat D 2007; 13 Suppl 3: S329–31.