# A study on the treatment of Parkinson's disease and cognitive impairment with multiple system atrophy by intranasal injection of insulin

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**Abstract.** Parkinson's disease (PD) and multiple system atrophy (MSA) are both common neurodegenerative diseases. To investigate the effects of intranasal insulin injection on motor function and cognitive impairment in patients with Parkinson's disease (PD) and multiple system atrophy (MSA).Thirteen PD patients and one MSA patient participated in the experiment . Using a random number table method, the participants were assigned to an experimental group (n=8) and a control group (n=6). The experimental group received insulin injection, while the control group received physiological saline injection. Both groups received nasal injection for 4 consecutive weeks. Compare the general information, language fluency (FAS), Montreal Cognitive Assessment Scale (MoCA), Beck Depression Inventory (BDI), and Parkinson's Unified Rating Scale (UPDRS) results between the two groups. Compared to the control group, the experimental group had a significantly higher FAS score, but there was no significant difference in the FAS score before and after treatment in the experimental group, and the prognosis score improved compared to before. In the experimental group, a MSA patient showed improvement in FAS scores during the four week treatment period, with no significant progression of the disease. There was no significant improvement in UPDRS score, BDI score, and MoCA score before and after treatment, the difference was not significant statistically. The use of insulin therapy for cognitive and motor disorders related to PD is safe and feasible. Intranasal insulin may improve functional motor function and cognitive performance in Parkinson's disease.

**Keywords:** Intranasal, insulin, Parkinson’s disease, UPDRS, MoCA, Multiple system atrophy.

## 1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease that mainly affects the elderly population. According to incomplete statistics, PD patients in China account for nearly half of the global incidence; among the elderly population aged 60 and above, the proportion of PD patients exceeds 1%. Parkinson's disease is characterized by a primary pathological alteration that involves the progressive loss of dopaminergic neurons in the substantia nigra of the midbrain, which results in a substantial reduction of dopamine levels in the striatum and the classic motor symptoms associated with the disorder. [1]. the risk factors for PD include genetic predisposition, environmental exposures, aging and oxidative stress. [2]. the clinical symptoms include static tremors, bradykinesia, posture and gait disorders, which bring great mental and economic pressure to families and society. Multiple system atrophy (MSA) is a rare neurodegenerative disease that mainly affects multiple systems such as the extrapyramidal system, cerebellum, autonomic nervous system, brainstem, and spinal cord. In the development process of MSA, PD is a common manifestation and may also appear in the early stages. Common clinical manifestations include urinary incontinence, frequent urination, and difficulty swallowing. At present, the pathogenesis of PD is not clear and mainly focuses on treatment and remission. In recent years, more and more evidence has shown that PD is associated with brain insulin resistance. Activating the signaling pathway of insulin in the brain and increasing insulin sensitivity in the brain may become a new direction for treating PD. Research has found that insulin is directly injected into the nasal mucosa through intranasal administration, allowing it to be absorbed by the blood, achieving the goal of increasing brain insulin concentration and improving insulin resistance. This method avoids the pain and risk of infection caused by subcutaneous injection, while

also achieving the peak concentration of absorbed drugs faster, allowing insulin to function more quickly. At the same time, due to the low systemic utilization rate of the systemic administration route, there is almost no effect on peripheral blood sugar. [5] The main pathway of insulin injection into the brain through the nasal cavity is through the intercellular gap of the olfactory nerve, which is transported along the trigeminal nerve and olfactory nerve branches to the brainstem area, significantly increasing the concentration of insulin receptors and increasing the concentration of insulin in the brain. This article investigates the relationship between Parkinson's disease and insulin resistance, and explores the feasibility and effectiveness of injecting insulin through nasal administration as a treatment for Parkinson's disease. Compared with traditional surgical methods, intranasal insulin is a non-invasive treatment method that can reduce surgical risk and postoperative recovery time. And it may have a neuroprotective effect, which can slow down or prevent the degeneration of dopamine neurons, thereby improving the symptoms of PD patients. The impact of intranasal insulin on cognitive ability in PD patients has not been elucidated. Therefore, this article studied the relationship between Parkinson's disease and insulin resistance, evaluated the cognitive and functional effects of taking 40 international units (IU) of insulin per day in adults with Parkinson's disease for four weeks compared to taking placebo, and explored the feasibility and effectiveness of injecting insulin through nasal administration as a treatment for Parkinson's disease.

## 2. Data sources and methods

### 2.1. Data sources

Select public data from 13 PD patients and 1 MSA patient who participated in the experiment at the University Of Massachusetts School Of Medicine in Massachusetts, USA.

### 2.2. Inclusion criteria for inclusion and exclusion indicators

① All patients meet the diagnostic criteria for Parkinson's disease and multiple system atrophy disease; ② the patient's condition is stable; ③ Informed consent of patients and their families. Exclusion criteria: ① Patients with missing clinical cases; ② Individuals who are allergic to insulin; ③ Individuals with organic lesions such as heart and brain. The study was reviewed and approved by the Ethics Committee.

### 2.3. Observation Method

This study was validated using a randomized, double-blind, placebo clinical trial method. The experimental group received nasal injection of 40 International Standard Units (IU) of insulin once a day, while the control group received daily saline placebo treatment. In a 4-week experiment, the motor function score, non-motor symptom score, and quality of life score were observed for pretreatment and prognosis. The experimenter completed screening visits, linear assessments, two follow-up visits, and end of treatment evaluations during the treatment period. The experimental evaluation included the Language Fluency Test (FAS), Parkinson's Unified Scale (UPDRS), Montreal Cognitive Assessment (MoCA), and Beck Depression Self-Assessment (BDI).

### 2.4. Statistical method

SPSS 25.0 statistical software was used for data processing, and statistical analysis was conducted on the data of the experimental group and the control group, including the general characteristics of the subjects, baseline, and post experimental effect analysis. The data that follows the normal distribution pattern is represented by (x changed to x with a bar above it, indicating the mean of $\bar{x} \pm s$), and one-way ANOVA was used for significance testing. It is believed that $P<0.05$ is a statistically significant difference.

# 3. Results

## 3.1. Demography

We divided the research subjects into two groups using the random number table method: the experimental group (n=8) and the control group (n=6). The experimental group comprised 6 males and 2 females, with an age range of 50 to 71 years and an average age of (63.25±2.18) years. The duration of Parkinson's disease ranged from 2 to 17 years with an average of (6.75±1.80) years. The control group comprised 3 males and 3 females, with an age range of 53 to 79 years and an average age of (62.17±3.91) years. The duration of Parkinson's disease in the control group ranged from 3 to 8 years with an average of (5.17±0.83) years. There was no statistically significant difference in general information between the two groups of patients (P>0.05).

**Table 1.**Comparison of General Information between Two Groups of Patients.

| GROUP | CASES | AGE | GENDER | DURATION OF ILLNESS | BMI |
|---|---|---|---|---|---|
| Placebo | 6 | 62.17±3.91 | 3/3 | 5.17±0.83 | 28.81 ±6.50 |
| Insulin | 8 | 63.25±2.18 | 6/2 | 6.88±0.52 | 23.90 ± 4.12 |
| Between Groups | | 0.80 | 0.37 | 0.30 | 0.67 |

## 3.2. Comparison of walking duration in exercise rehabilitation between two groups of patients

According to the comparison of information statistics, the exercise rehabilitation status of the two groups of patients indicates that the pre-intervention and post-intervention walking duration of the control group exceed that of the experimental group, yet no significant difference was observed between the two groups; There was no significant difference in the number of walking steps between the experimental group and the control group. After 4 weeks of INI treatment, the walking duration of PD patients improved, but there was no significant intra group difference between pretreatment and prognosis; The prognosis of both groups showed a decrease in walking steps compared to before, as shown in Table.2.

**Table 2.** Comparison of exercise rehabilitation between two groups of patients before and after the experiment.

| Cases | Walking Time | | | Walking steps | | |
|---|---|---|---|---|---|---|
| | Baseline | Post-Treatment | Within insulin group | Baseline | Post-treatment | Within placebo group |
| Placebo | 4.35±0.15 | 4.57±0.27 | 0.16 | 7.33±0.49 | 7.00±0.37 | 0.17 |
| Insulin | 3.76±0.28 | 4.04±0.39 | 0.57 | 7.19±0.67 | 6.88±0.52 | 1.00 |
| Between Groups | 0.12 | 0.30 | | 0.87 | 0.86 | |

## 3.3. Comparison of language fluency (FAS) between two groups of patients

FAS refers to participants being asked to speak words starting with the letters F, A, and S within one minute. According to the comparison of the language fluency between the two groups based on information statistics, it is noteworthy that the control group exhibited significantly inferior performance compared to the experimental group during the treatment phase. This observation, coupled with our previous findings, provides evidence that the experimental intervention had a positive impact on the experimental group's performance. After receiving INI treatment, the language fluency of the experimental group improved. In the comparison of language fluency, a significant divergence was observed between the groups before and after treatment but the results were not statistically significant, as shown in Table.3.

**Table 3.** Comparison of FAS status between two groups of patients before and after the experiment.

| Cases | Baseline | Post-Treatment | Inter Groups |
|---|---|---|---|
| Placebo | 32.83±0.95 | 30.83±2.92 | 0.49 |
| Insulin | 38.75±2.04 | 41.00±2.90 | 0.37 |
| Between Groups | 0.04 | 0.03 | |

### 3.4. Comparison of cognitive assessment scale disorders between two groups of patients

The Montreal Cognitive Assessment (MoCA) is an assessment tool used for rapid screening of mild cognitive impairment. The total score of the cognitive domain scale is 30 points, and the test results show a normal value of ≥ 26 points. In the Montreal Cognitive Assessment (MoCA) test, both groups of patients had normal levels of cognitive impairment, and both groups improved during the treatment process. However, there was no statistically significant difference between the two groups (P>0.05), as shown in Table.4.

**Table.4.** Comparison of MOCA between two groups of patients' cognitive assessment scales before and after the experiment.

| Cases | Baseline | Post-Treatment | Inter Groups |
|---|---|---|---|
| Placebo | 26.83±1.05 | 28.17±2.32 | 0.31 |
| Insulin | 27.93±0.55 | 28.00±1.07 | 0.17 |
| Between groups | 0.08 | 0.86 | |

### 3.5. Comparison of the Unified Parkinson's Disease Rating Scale (UPDRS) between two groups of patients

The Unified Parkinson's Disease Rating Scale (UPDRS) is utilized for clinical evaluation of the impact of PD on motor, cognitive, and other functions. The summary of UPDRS sub scores is as follows: UPDRS - i intellectual, emotional, and motivational disorders; UPDRS-II: Diet, Activities of Daily Living, Walking, and Balance; UPDRS-III language, tremors; slow movement, finger tapping, unstable posture, slow body movement, and movement disorders. In UPDRS I, the control group's non-motor symptoms were higher than those in the experimental group, but neither group showed significant improvement during the treatment period; In the Updrs II section, there was no improvement in the living state function of the experimental group before and after treatment, while the living state function of the control group was better than that of the experimental group; In the Updrs III section, the motor symptom score of the experimental group was better than that of the control group. Before and after treatment, there was no significant improvement in the motor state function of the control group, and the experimental group also showed a decrease. The improvement in motor symptoms in the experimental group was statistically significant compared to before and after treatment (P<0.05); In the Bradykinesia section, both the experimental group and the control group showed a decrease in complication scores, and there was no significant improvement in treatment, as shown in Table.5.

**Table 5.** Comparison of UPDRS between two groups of patients before and after the experiment using the unified Parkinson's disease comprehensive score table.

| CASES | TIME AND SIGNIFICANCE | UPDRS I | UPDRS II | UPDRS III | BRADYKINESIA |
|---|---|---|---|---|---|
| **Insulin** | baseline | 9.60±3.90 | 13.90±10.10 | 31.50±20.00 | 13.10±10.90 |
| | post-treatment | 8.12±4.30 | 13.50±10.80 | 25.60±21.80 | 10.30±10.90 |
| | inter groups | 0.07 | 0.64 | 0.02 | 0.08 |
| **Placsebo** | baseline | 11.70±3.90 | 15.30±8.20 | 31.70±13.30 | 14.42±8.20 |
| | post-treatment | 12.00±1.60 | 14.00±8.20 | 30.50±15.80 | 12.80±7.70 |
| | inter groups | 1.00 | 0.18 | 0.27 | 0.82 |
| **Between groups** | | 0.08 | 0.89 | 0.84 | 0.76 |

## 4. Discussion

Parkinson's disease (PD) is a prevalent neurological condition that primarily affects individuals in middle and advanced age, also known as tremor paralysis. Its main clinical symptoms are static tremors, motor delays, muscle rigidity, and postural gait disorders [6]. The incidence rate of PD is 15/100000 people, and the number of Parkinson's patients in China has exceeded 200000. [7] At the same time, the incidence rate tends to increase with age, and the incidence rate of PD in men is higher than that in women. For the treatment of PD, the main focus is currently on alleviating symptoms. Common treatment methods include medication, physical therapy, and surgical treatment. In recent years, studies have shown a significant decrease in insulin receptor mRNA expression in the SN dense region of PD patients, leading to an increase in brain insulin resistance [8]. In this study, we aimed to investigate the therapeutic effect and safety of intranasal insulin therapy for cognitive impairment in patients with Parkinson's disease. To achieve this, we employed a randomized, double-blind, placebo-controlled clinical trial design to objectively verify the efficacy and safety of the therapy. A total of 15 PD patients and 1 MSA patient were included and randomly assigned to either the experimental group or the control group. The experimental group received nasal injections of 40 International Standard Units (IU) of insulin once a day, while the control group received daily saline placebo treatment. In a 4-week experiment, the motor function score, non-motor symptom score, and quality of life score were observed for pretreatment and prognosis. The experimenter completed screening visits, linear assessments, two follow-up visits, and end of treatment evaluations during the treatment period. The experimental evaluation included a language fluency test, The Unified Parkinson's Scale (UPDRS), the Montreal Cognitive Assessment Scale (MoCA), and the Beck Depression Self Rating Scale (BDI-II) were employed to quantitatively assess Parkinson's disease patients' motor symptoms, cognitive functions, and depressive symptoms, respectivel. The data is sourced from an open dataset independent laboratory at the University Of Massachusetts School Of Medicine in Worcester, Massachusetts, USA. Experimental results show that the FAS score of the experimental group is significantly higher than that of the control group, suggesting that the experimental group's language fluency is significantly better than that of the control group; There was no significant difference in FAS between the experimental group before and after treatment, but according to the results, it was found that the prognosis score improved compared to beforeIn Drosdowsky et al.'s study, they investigated the effect of insulin on language fluency in Parkinson's disease patients. By administering daily insulin injection therapy to 15 Parkinson's disease patients and evaluating their language fluency, the results showed that the language fluency score of the insulin treatment group was significantly higher than that of the control group [9], consistent with the conclusion of this article. One patient in the experimental group had MSA, and during the four week treatment, their language fluency improved without significant progression. In addition, this study found that there was no significant improvement in various parts of UPDRS scores, walking duration, and cognitive impairment both before and after treatment, yet the difference was not statistically significant. In Mady CHHEDROFF's article, it was pointed out that there was no improvement in cognitive function of PD patients after intranasal administration of insulin [10]. The author believes that as a chronic neurological disease, PD is related to the dosage of insulin used, ethnicity, and number of cases, making it difficult to observe its changes in the short term.

## 5. Conclusion

In summary, nasal injection of insulin activates the brain insulin pathway, which can improve patients' language fluency and quality of life, and has high safety. It may become one of the new methods for treating PD. However, this experiment also possesses some limitations. Due to the small sample size, this study is unable to perform extensive statistical analysis on factors such as disease course, drugs, and other unrelated variables. In addition, this study did not observe long-term treatment for patients, and it is not possible to determine the long-term efficacy of intranasal insulin injection on PD. In future research, further exploration should be conducted on the efficacy and safety

of intranasal insulin injection in PD patients. Larger scale experiments and long-term follow-up observations are needed to provide more sufficient evidence for clinical research.

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