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Original article

Levodopa and pramipexole combination therapy efficacy in Vietnamese patients with Parkinson's disease: a randomized controlled trial

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Abstract: Early diagnosis and appropriate treatment of Parkinson's disease to minimize the adverse effects of the disease and drug side effects on the patient. Using levodopa combined with pramipexole is an effective therapy for treating Parkinson's disease.
Objectives — This study aims to evaluate the treatment outcome of combination therapy with levodopa and pramipexole compared to levodopa monotherapy in Vietnamese Parkinson's patients.
Material and Methods — A randomized controlled clinical trial with a 1:1 randomized ratio of 80 individuals with Parkinson's disease. The intervention group received a combination therapy with levodopa/benserazide and pramipexole, and the control group received a monotherapy with levodopa/benserazide. Motor symptoms, non-motor symptoms, The Unified Parkinson's Disease Rating (UPDRS), and The Parkinson's Disease Questionnaire (PDQ-39) scores were assessed before, after, and a follow-up period of 1 and 4 weeks after discharge to evaluate the treatment outcome.
Results — Combining therapy with levodopa and pramipexole led to statistically significant improvements in UPDRS and PDQ-39 scores ($p<0.05$). The mean difference in UPDRS parts I, II, and III after 4 weeks of discharge was -0.5 ($p=0.014$), -1.68 ($p=0.005$), and -2.52 ($p=0.010$) respectively. The quality of life was also enhanced by combining therapy due to a better reduction of PDQ-39 score: 26.0±6.3 versus 32.7±6.4 ($p<0.001$). The most common side effects were headache, nausea/vomiting, and somnolence.
Conclusions — Treatment with levodopa combined with pramipexole improves clinical symptoms and quality of life in patients with Parkinson's, as evidenced by improvements in UPDRS and PDQ-39 scores.

Keywords: Parkinson's disease, levodopa, pramipexole, The Unified Parkinson's Disease Rating, The Parkinson's Disease Questionnaire, randomized controlled clinical trial.

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Introduction

Parkinson's disease is a complex and widespread central nervous system disorder, ranking second worldwide in neurodegenerative diseases after Alzheimer's [1]. Parkinson's disease was identified as slow movement, muscle stiffness, tremor at rest, and a shuffling gait [2]. World Health Organization report in 2019 showed over 8.5 million patients with Parkinson's disease, and the prevalence had doubled in the past 25 years [3]. The prevalence of Parkinson's disease was increasing due to longer life expectancy, and it was projected to affect over 50% more individuals by 2030 [4]. Although Parkinson's disease is not life-threatening, it significantly impacts the quality of life (QoL). In addition, a study of Vietnamese Parkinson's patients' QoL (2021) in the ability to walk and daily activities reported poor outcomes (Mean PDQ-39 of 49.4±30.5) [5]. Therefore, early diagnosis and appropriate treatment are crucial in minimizing the adverse effects of the disease and its associated medication side effects [6].

Various methods for treating Parkinson's disease have been studied including physical therapy, speech therapy, psychotherapy, and medication. In addition, a new trend in physical therapy is treadmill exercise, which is still being studied and has not been applied in humans yet [7]. However, medication is still the major way to enhance the symptoms of Parkinson's patients. Specifically, combining levodopa and pramipexole effectively improves daily activities, clinical symptoms, and disease severity. Several randomized controlled trials (RCTs) have demonstrated that combination therapy provides more pronounced effects and fewer side effects compared to levodopa monotherapy [8, 9]. Some studies have even suggested that combining pramipexole and levodopa does not significantly reduce the incidence of adverse events. However, few studies on the Vietnamese population that compared levodopa monotherapy and combination with pramipexole led to missing data for drug and therapy selection. This study aims to evaluate the treatment outcome of combination therapy with levodopa and pramipexole compared to levodopa monotherapy for therapy selection in Vietnamese Parkinson's patients.

Material and Methods

Study design and population

We conducted a randomized controlled trial, parallel-group, randomization ratio of 1:1 in patients with Parkinson's disease admitted to Can Tho Central General Hospital from March 2021 to May 2023.

Inclusion criteria: according to The United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) [10], patients with Parkinson's disease had (1) bradykinesia and (2) muscle rigidity or tremor or postural disturbances; (3) Consented to participate in the study.

Exclusion criteria: (1) allergies or contraindications to the drugs used in the study; (2) individuals with mental illness; (3) poor adherence to therapy; (4) heart, liver, or kidney failure, and drug addicts; (5) secondary Parkinson's syndrome, atypical clinical signs, unresponsiveness to levodopa; (6) imaging studies indicated the presence of encephalitis, cerebrovascular disease, hydrocephalus, or dementia.

Sample size

The sample size was calculated based on the Yu-Young Ting study [11], the prevalence of monotherapy effectiveness with Madopar 250mg (levodopa 200mg and benserazide 50mg was 26.19% (p^1=0.2619), and combination therapy with Madopar 250mg plus pramipexole 0.25mg was 43.18% (p^2=0.4318). We calculated n=40 with α=0.1 and β=0.5, c (α, β)=2.7. We conducted a study on 80 outpatients.

Data collection and intervention methods

Enrolled patients were randomized into two groups, (Control and Intervention) and were numbered from small to large, respectively, and equally distributed with a ratio of 1:1. We conducted a single-blind, meaning that outpatients were unaware of the two therapies. The control group received half a tablet of levodopa/benserazide 200/50 mg three times a day, to be taken with food. The dosage could be increased to 1.5 to 3 tablets as needed. The study group received the same regimen of levodopa/benserazide and additionally pramipexole 0.25mg, half a tablet taken twice daily. The patient had the right to discontinue if side effects, such as dizziness, vomiting, diarrhea, or other adverse reactions occurred after the side effects subsided. The treatment duration was four weeks for both groups.

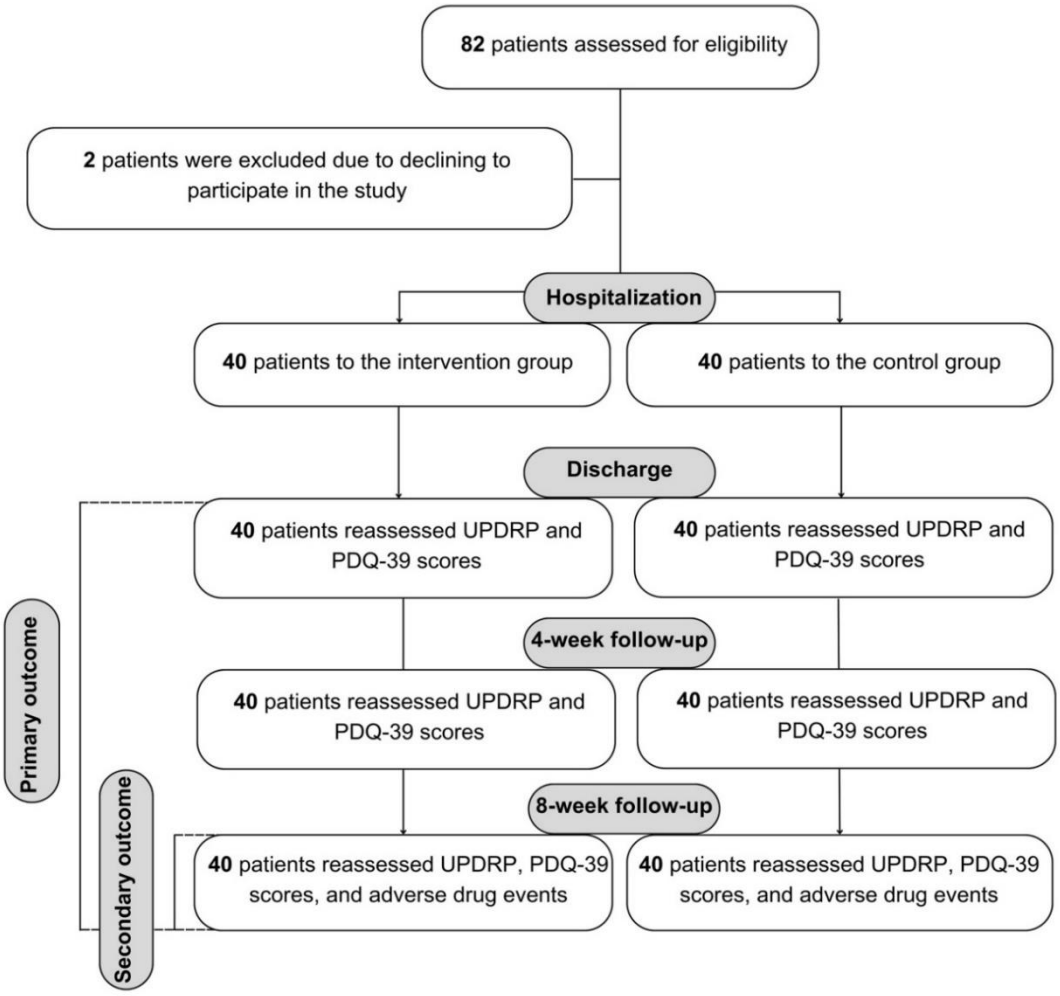

Figure 1. Flowchart of the study population.

UPDRS, The United Kingdom Parkinson's Disease Society Brain Bank; PDQ, The Parkinson's Disease Questionnaire.

Table 1. Baseline clinical characteristics

Characteristic		*Total (n=80)*		*Control group (n=40)*		*Intervention group (n=40)*		*p[a]*
		n	%	n	%	n	%	
Gender	Men	27	33.8	10	25.0	17	57.5	0.09
	Women	53	66.3	30	75.0	23	42.5	
Age	Mean ± SD	72.16 ± 10.50		74.15 ± 9.23		70.18 ± 11.40		0.09[b]
	<60	10	12.5	2	5.0	8	20.0	0.04*
	≥60	70	87.5	38	95.0	32	80.0	
Motor symptoms	Tremor	76	95.0	38	95.0	38	95.0	1.00
	Bradykinesia	78	97.5	39	97.5	39	97.5	1.00
	Muscle Rigidity	75	93.8	37	92.5	38	95.0	0.64
	Postural disturbances	39	48.8	20	5.0	19	47.5	0.82
	Other	2.0	2.4	2.0	5.0	0.0	0.0	0.15
Non-motor symptoms	Olfactory dysfunction	7	8.8	4	10.0	3	7.5	0.69
	Cognitive impairment	22	27.5	11	27.5	11	27.5	1.00
	Pain and sensory disturbances	75	93.8	37	92.5	38	95.0	0.64
	Autonomic disorders	75	93.8	37	92.5	38	95.0	0.64
	Restless legs syndrome	23	28.8	11	27.5	12	30.0	0.80
	Constipation	49	61.3	26	65.0	23	57.5	0.49
Risk factors	Family history	3	3.8	2	5.0	1	2.5	0.56
	Cranium injury history	5	6.3	4	10.0	1	2.5	0.17
	Toxic exposure	5	6.3	3	7.5	2	5.0	0.64
Relieving factors	NSAID using	57	71.3	30	75.0	27	67.5	0.46
	Estrogen using	18	22.5	13	32.5	5	12.5	0.03*
UPDRS-score	UPDRS-I	8.4 ± 1.7		8.4 ± 1.7		8.5 ± 1.8		0.75[b]
	UPDRS-II	21.5 ± 3.6		21.8 ± 4.1		21.2 ± 3.8		0.50[b]
	UPDRS-III	37.1 ± 4.5		37.1 ± 4.9		37.0 ± 4.0		0.88[b]
	UPDRS-IV	5.6 ± 2.3		5.6 ± 2.3		5.7 ± 2.5		0.85[b]
	Total	72.6 ± 10.4		72.8 ± 11.6		72.4 ± 9.3		0.84[b]
PDQ-39 score		49.1 ± 5.8		49.3 ± 5.7		48.9 ± 6.0		0.77[b]

Control group: levodopa/benserazide 200/50 mg, Intervention group: levodopa/benserazide 200/50 mg and additionally pramipexole 0.25mg. UPDRS, The United Kingdom Parkinson's Disease Society Brain Bank; PDQ, The Parkinson's Disease Questionnaire; SD, standard deviation. [a] Chi-squared test; [b] Independent Samples t-test; * statistical significance.

All patients enrolled in the study were examined for medical and drug use history, general and clinical characteristics by medical practitioners after, before the treatment, and after 1 to 4 weeks of follow-up. Motor symptoms and non-motor symptoms were assessed using the following criteria: Motor symptoms: Tremor (resting tremor in the extremities, exacerbated by emotional stress, improved by intentional movement), bradykinesia (slowness and difficulty in initiating movement), muscle rigidity (stiffness or hypertonia), cogwheel rigidity, postural disturbances, and other motor abnormalities. Non-motor symptoms: Olfactory dysfunction, cognitive impairment, mood disorders (depression, anxiety, apathy), pain and sensory disturbances, autonomic disorders (orthostatic hypotension, urinary urgency, urinary incontinence), restless legs syndrome, and constipation. Risk factors were collected through interviews for family history, cranium injury history, and toxic exposure. Relieving factors included medication history of using NSAID and using estrogen replacement therapy in postmenopausal women [12].

The Unified Parkinson's Disease Rating Scale [13] (UPDRS) parts I, II, and III assessed mental status, daily activities, and motor symptoms before and after 4 weeks of treatment, with lower scores indicating fewer symptoms. The Parkinson's Disease Questionnaire (PDQ)-39 [14] was used to assess quality of life before and after treatment, with higher scores indicating lower quality of life.

Data on toxic side effects, including headache, vomiting/nausea, somnolence, dizziness, hallucinations, diarrhea, and dyskinesias, were also collected for both treatment groups.

Study outcome

The primary outcome was to evaluate the efficacy of combination therapy with levodopa/benserazide 200/50 mg and pramipexole 0.25mg compared to monotherapy with levodopa/benserazide 200/50 mg in symptom-relieving, reducing UPDRS (I, II and III), and enhancing QoL. The secondary outcome was also assessed through adverse drug events and all-cause mortality (if any) after four weeks of treatment.

Data analysis

Data were collected and processed by the SPSS 20.0 software. Quantitative variables with normal distribution were described by mean ± standard deviation (SD), and non-normal distribution variables were characterized by the median, maximum, minimum, and interquartile range (IQR). Qualitative variables are represented by rate and percentage. The difference between two qualitative variables was characterized by the Chi-squared test; normally distributed quantitative variables were analyzed by simple t-test (if two groups were analyzed) or ANOVA (if ≥ three groups were investigated); quantitative variables were analyzed with non-normal distribution by Mann-Whitney test (if 2 groups studied) or Kruskal-Wallis test (if ≥ three groups were analyzed); $p<0.05$ implied statistical significance. We used the risk ratio (RR) to analyze treatment results between the intervention and control groups.

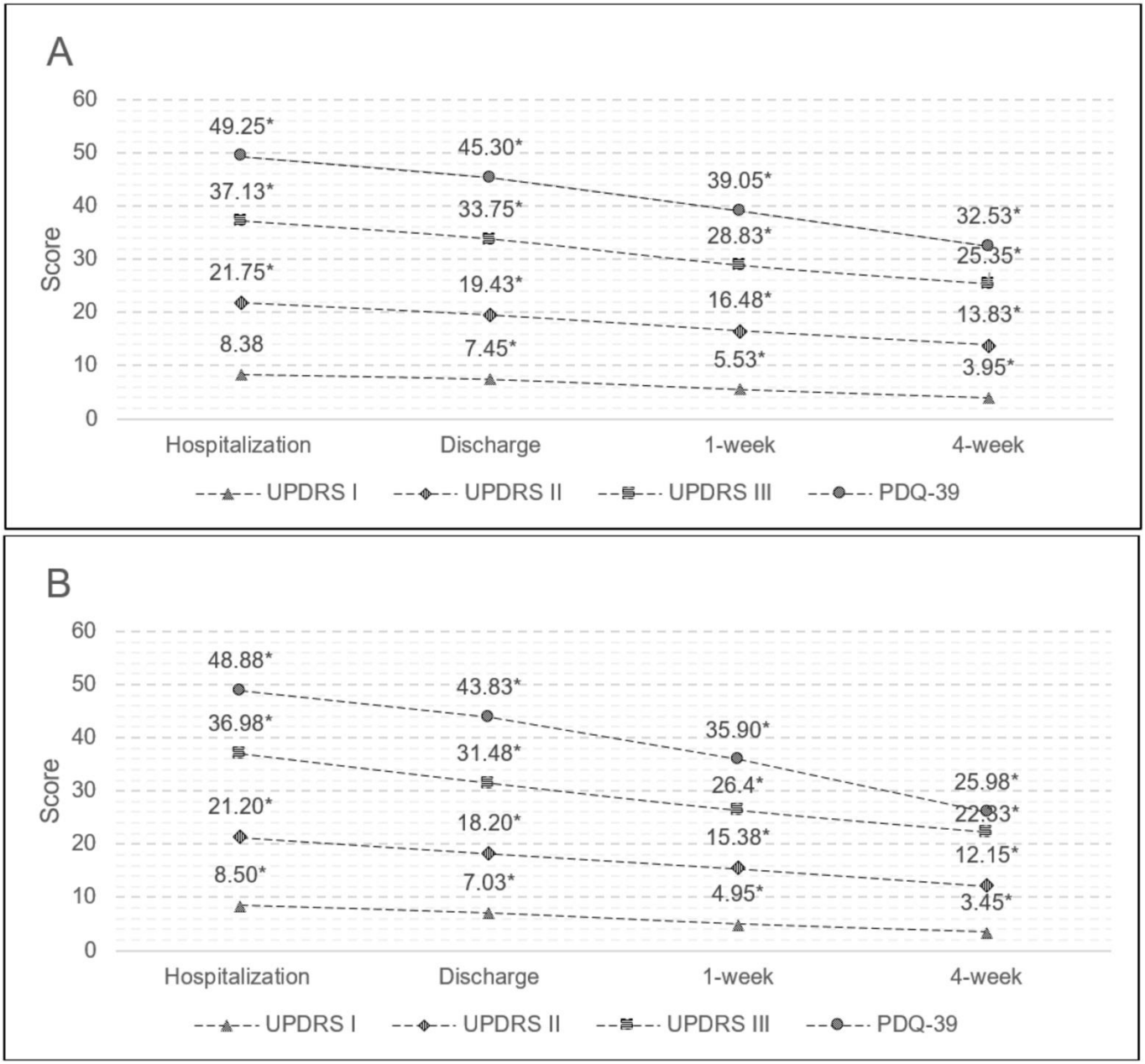

Figure 2. UPDRS and PDQ-39 score changes during the treatment periods (A) In the control group, (B) In the intervention group.

Control group: levodopa/benserazide 200/50 mg, Intervention group: levodopa/benserazide 200/50 mg and additionally pramipexole 0.25mg. UPDRS, The United Kingdom Parkinson's Disease Society Brain Bank; PDQ, The Parkinson's Disease Questionnaire. * statistical significance (p<0.001).

Results

General characteristics

Of 82 individuals with Parkinson's disease hospitalization, 2 patients declined to participate in the study. 80 patients were randomized into two treatment groups: control group (n=40) and intervention group (n=40) (*Figure 1*).

The control group consisted of 10 men and 30 women, with an average age of 74.2±9.2 years. The intervention group consisted of 17 men and 23 women, with an average age of 70.2±11.4 years. There were no significant differences in age or sex (*Table 1*). The study found that the common motor symptoms observed in both the control and study groups were bradykinesia, muscle rigidity, and tremor. It is mentioned that there were no significant differences in these motor symptoms between the two groups. This suggested that both groups had similar baseline motor symptoms before the treatment intervention (*Table 1*). The study also identified common non-motor symptoms in both the control and study groups, including pain, sensory disturbance, autonomic dysfunction, and constipation. No significant differences were found in such non-motor symptoms between the two groups. This implied that the baseline non-motor symptoms were comparable in both groups prior to the treatment intervention (*Table 1*).

Table 2. Changes in symptoms within groups

Symptom relieving	*Total (n=80)*		*Control group (n=40)*		*Intervention group (n=40)*		*RR*	*(95% CI)*	*p[a]*
	n	%	n	%	n	%			
Discharge									
Tremor	46	57.5	24	52.2	22	47.8	0.92	(0.63;1.34)	0.65
Bradykinesia	52	65.0	25	62.5	27	67.5	1.08	(078; 1.50)	0.64
Muscle Rigidity	47	58.8	22	55.0	25	62.5	1.14	(0.79;1.64)	0.50
Autonomic disorders	45	56.3	23	57.5	22	55.0	0.96	(0.65;1.41)	0.82
Constipation	40	50.0	21	52.5	19	47.5	0.90	(0.58;1.40)	0.65
Pain and sensory disturbances	45	56.3	21	52.5	24	60.0	1.14	(0.77;1.68)	0.50
1-week									
Tremor	57	71.3	26	65.0	31	77.5	1.19	(0.90;1.58)	0.22
Bradykinesia	56	70.0	27	67.5	29	72.5	1.07	(0.81;1.43)	0.63
Muscle Rigidity	54	67.5	25	62.5	29	72.5	1.16	(0.85;1.58)	0.34
Autonomic disorders	53	66.3	25	62.5	28	70.0	1.12	(0.82;1.53)	0.48
Constipation	42	52.5	22	55.0	20	50.0	0.91	(0.60;1.38)	0.65
Pain and sensory disturbances	52	65.0	25	62.5	27	67.5	1.08	(0.78;1.49)	0.64
4-week									
Tremor	67	83.8	30	75.0	37	92.5	1.23	(1.01;1.50)	0.03*
Bradykinesia	65	81.3	31	77.5	34	85.0	1.10	(0.89;1.35)	0.39
Muscle Rigidity	64	80.0	28	70.0	36	90.0	1.29	(1.02;1.61)	0.02*
Autonomic disorders	66	82.5	30	75.0	36	90.0	1.20	(0.98;1.47)	0.07
Constipation	46	57.5	24	60.0	22	55.0	0.92	(0.63;1.34)	0.65
Pain and sensory disturbances	62	77.5	27	67.5	35	87.5	1.30	(1.01;1.66)	0.03*

Control group: levodopa/benserazide 200/50 mg, Intervention group: levodopa/benserazide 200/50 mg and additionally pramipexole 0.25mg. RR, risk ratio. [a] Chi-squared test.

Table 3. Changes in UPDRS and PDQ-39 score within groups

Variables		Total (n=80)	Control group (n=40)	Intervention group (n=40)	p[a]
Discharge					
UPDRS	I	7.2±1.4	7.4±1.3	7.0±1.4	0.164
	II	18.8±3.3	19.4±3.5	18.2±3.0	0.096
	III	32.6±4.8	33.7±4.5	31.5±4.8	0.033
PDQ-39		44.6±5.3	45.3±5.2	43.8±5.3	0.215
1-week					
UPDRS	I	5.2±1.2*	5.5±1.2*	4.9±1.1*	0.030
	II	15.9±2.5*	16.5±2.4*	15.4±2.5*	0.047
	III	27.6±5.2*	28.8±4.9*	26.4±5.3*	0.037
PDQ-39		37.5±6.0*	39.0±5.8*	35.9±5.9*	0.019
4-week					
UPDRS	I	3.7±0.9*	3.9±0.8*	3.4±0.9*	0.014
	II	13.0±2.7*	13.8±2.1*	12.1±3.0*	0.005
	III	23.8±5.3*	25.3±4.5*	22.3±5.7*	0.010
PDQ-39		29.4±7.1*	32.7±6.4*	26.0±6.3*	<0.001

Control group: levodopa/benserazide 200/50 mg, Intervention group: levodopa/benserazide 200/50 mg and additionally pramipexole 0.25mg. UPDRS, The United Kingdom Parkinson's Disease Society Brain Bank; PDQ, The Parkinson's Disease Questionnaire. * statistical significance (p<0.001) compared with scores obtained before treatment within the group. [a] Independent Samples T-test.

Table 4. Side effects after 4 weeks of treatment

Side effected	*Total (n=80)*		*Control group (n=40)*		*Study group (n=40)*		*p[a]*
	n	%	n	%	n	%	
Headache	9	11.2	4	10.0	5	12.5	0.72
Vomiting/nausea	8	10.0	5	12.5	3	7.5	0.46
Somnolence	9	11.2	5	12.5	4	10.0	0.72
Dizziness	3	3.7	2	5.0	1	2.5	0.56
Hallucinations	1	1.2	0	0.0	1	2.5	0.31
Diarrhea	5	6.2	3	7.5	2	5.0	0.64
Dyskinesias	5	6.2	2	5.0	3	7.5	0.64

Control group: levodopa/benserazide 200/50 mg, Intervention group: levodopa/benserazide 200/50 mg and additionally pramipexole 0.25 mg. [a] Chi-squared test.

Treatment efficacy

Figure 2 showed changes in UPDRS and PDQ-39 scores during the treatment periods; both groups showed treatment effectiveness in symptom-relieving (p<0.001). However, the intervention group showed better outcomes (*Figure 2*).

The intervention group improved treatment outcomes in relieving symptoms, especially in the four-week evaluation. Treatment with combination therapy relieved tremor (RR=1.23, 95% CI: 1.01-1.50, p=0.03), muscle rigidity (RR=1.29, 95% CI: 1.02-1.61, p=0.02), and pain (RR=1.30, 95% CI: 1.01-1.66, p=0.03) with statistically significant. Constipation was the only symptom that did not show a better outcome in the intervention group compared to the control group (RR=0.92, 95% CI: 0.63-1.34, p=0.65) (*Table 2*). However, it was insignificant, and both groups had decreased constipation symptom proportion during the study duration.

Before treatment, the study found no significant difference in the mean scores of UPDRS sections I, II, and III between the control and study groups. However, after treatment, both groups showed a significant reduction in the mean scores of UPDRS parts I, II, and III compared to before treatment (p<0.05). Additionally, the study group exhibited significantly greater reductions in the mean scores of UPDRS parts I, II, and III compared to the control group. These results suggested that the combination therapy of levodopa and pramipexole had a more pronounced effect on reducing motor symptoms in the study group compared to the control group (*Table 2*). Before treatment, there was no significant difference in PDQ-39 scores between the two groups. In contrast, the mean PDQ-39 score decreased significantly in both groups after treatment (p<0.05) (*Figure 2*). Furthermore, after treatment, the PDQ-39 score was significantly lower in the study group than in the control group (p<0.05), (*Table 3*).

Table 5. Treatment outcome compared to other studies

Study	*Duration*	*Evaluation score*	*Mean difference*	*p*
De-Qi Jiang (2020), n=3017, [9]	8-12-week	UPDRS part I	-2.20	<0.001
		UPDRS part II	-1.65	<0.001
		UPDRS part III	-1.41	<0.001
		UPDRS part IV	-1.60	<0.001
Yan Wang (2021), n=2171, [8]	12-16-week	UPDRS part I	-1.02	<0.001
		UPDRS part II	-1.26	<0.001
		UPDRS part III	-1.31	<0.001
		UPDRS part IV	-1.54	<0.001
Yu Yong-ting (2016), n=86, [11]	Discharge	UPDRS part I	-1.30	<0.05
		UPDRS part II	-3.10	<0.05
		UPDRS part III	-4.00	<0.05
	6-month	UPDRS part I	-1.4	<0.05
		UPDRS part II	-2.3	<0.05
		UPDRS part III	-3.2	<0.05
Our study (2023), n=80	Discharge	UPDRS part I	-0.42	0.164
		UPDRS part II	-1.23	0.096
		UPDRS part III	-2.27	0.033
		PDQ-39	-1.47	0.215
	1- week	UPDRS part I	-0.58	0.030
		UPDRS part II	-1.1	0.047
		UPDRS part III	-2.43	0.037
		PDQ-39	-3.15	0.019
	4-week	UPDRS part I	-0.5	0.014
		UPDRS part II	-1.68	0.005
		UPDRS part III	-2.52	0.010
		PDQ-39	-6.55	<0.001

UPDRS, The United Kingdom Parkinson's Disease Society Brain Bank; PDQ, The Parkinson's Disease Questionnaire.

The study evaluated the occurrence of side effects in both the control and study groups. The reported side effects included headache, vomiting/nausea, somnolence, dizziness, hallucinations, diarrhea, and dyskinesia. It is mentioned that the rate of side effects in the two groups was not statistically significant. This implied no significant differences in the occurrence of these side effects between the control group and the study group (*Table 4*).

Discussion

Principal findings

The primary outcome was to evaluate the efficacy of combination therapy compared to monotherapy in symptom-relieving, reducing UPDRS (I, II, and III), and enhancing QoL. Our results suggested that the combination therapy of levodopa and pramipexole had a more pronounced effect on reducing motor symptoms in the study group compared to the control group. After the study period, both groups showed a significant reduction in the mean scores of UPDRS parts I, II, III, and PDQ-39 compared to before treatment (p<0.001). The intervention group exhibited significantly greater reductions in the mean scores of UPDRS parts I, II, III, and PDQ-39, especially the activities of daily living UPDRS score with a mean difference of -1.68 (p=0.02) (as shown in Tab. 2). Side effects were evaluated during a four-week follow-up. Our result showed no difference within groups, which indicated the safety of combination therapy with one drug addition.

Strengths and weaknesses of the study

Our study had a sample collection process with a straightforward design, including and excluding criteria. All study participants volunteered and benefited from the study. The design of the intervention study closely followed the checklists of Consolidated Standards of Reporting Trials (CONSORT) 2010. Study methods were clearly described and reproducible. The intervention results of the study clearly showed the differential effect between the two groups. Our study also evaluated the adverse drug events of the therapy over three periods (discharge, one-week and four-week follow-ups). Both combination therapy and monotherapy were safe for use in patients. Therefore, our data could be a reference for further studies. In addition, similar studies in the Vietnamese population had not been recorded for publication. Our study could be used as medical evidence to choose and ensure the safety of the treatment in the Vietnamese population.

However, our study was evaluated only in one hospital, which could lead to bias in baseline characteristics. Therefore, a multicenter study with a similar or larger sample size is required to better represent the study population. In our research, with a follow-up period of four weeks, patients could use the therapy longer than the evaluation period. Therefore, a study with a more extended evaluation period is needed to give more substantial evidence for the efficacy and safety effects of the two regimens.

Possible explanations and comparison with other studies

The study observed that the main motor symptoms of Parkinson's disease included bradykinesia, muscle rigidity, and resting tremors (*Table 1*). Postural disturbances were less common, while other symptoms, such as salivation and eyelid spasms, were observed in a small number of patients. Non-motor symptoms were also documented, including pain, sensory disturbances, autonomic disorders, constipation, cognitive impairment, restless legs syndrome, and olfactory disturbances. The motor manifestations of Parkinson's disease are thought to result from imbalances in neurotransmitters, particularly dopamine and acetylcholine, within the basal ganglia and its connections. In idiopathic Parkinson's syndrome, the loss of dopamine in the substantia nigra disrupts the normal balance between these neurotransmitters, leading to symptoms of hypoactivity. After treatment, the symptom-relieving outcome of combination therapy was more effective than monotherapy, especially in pain symptoms (Absolute difference in proportion was 20%, RR=1.3, 95% CI of 1.01-1.66, p=0.03), followed by tremor and muscle rigidity (*Table 2*).

One week after discharge, our study showed a significant difference in enhancing UPDRS and PDQ-39 scores between groups, and the data was described as a better outcome at a four-week follow-up period (*Table 3*, *5*). The results were similar to other studies with different follow-up periods. A systematic review of De-Qi Jiang (2020) in 3017 patients within 29 RCTs showed the mean difference after followed-up periods between groups in UPDRS I, II, and III scores was -2.20, -1.65, and -1.41 respectively (p<0.001) [9]. Another systematic review by Yan Wang (2021) showed a consistent outcome in 2171 patients within 24 RCTs [8]. Other RCTs by Jingzhong Huang (2018) and Yu Yong-ting (2016) also indicated a significant difference in reducing UPDRS scores in the combination group compared to the control group [11] (*Table 5*). Combination therapy of levodopa and pramipexole was more effective in reducing the UPDRS and PDQ-39 scores that were considered for improving treatment outcomes, relieving symptoms, and enhancing the quality of life. Therefore, our study outcome confirmed the optimal and differentiated treatment effectiveness of combination therapy in the Vietnamese population.

Through our study, the most common side effects were headache, nausea/vomiting, and somnolence. However, the rate of side effects was not high and not severe. Furthermore, the incidence of side effects between levodopa monotherapy versus the combination of pramipexole and levodopa was no different (*Table* 4). Similar findings were reported in previous studies, demonstrating the therapeutic advantage of combining levodopa and pramipexole in reducing symptoms and improving the quality of life in Parkinson's patients [11]. Therefore, this finding implied the safe use of both therapies for patients. Especially in the Vietnamese population, levodopa monotherapy or combination with pramipexole was safe for Parkinson's patients.

Conclusion

Combination therapy with levodopa and pramipexole has shown a better treatment outcome in improving clinical symptoms and quality of life, as evidenced by improvements in UPDRS score and PDQ-39 score. The incidence of side effects was comparable between the combination therapy group and the levodopa monotherapy group. The safety of the two therapies was described as low in rate and non-severe in side effects.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was reviewed and approved by the Scientific Research Council and the Medical Ethics Council of Can Tho University of Medicine and Pharmacy, with approval number 220/PCT/HĐĐĐ. Written informed consent was obtained from all study participants. Enrolled participants had to sign their names on the document.

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Conflict of interest

There was no conflict of interest in our study.

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