Original Article

Comparative Efficacy of Fludrocortisone versus Midodrine for the Treatment of Orthostatic Hypotension in Parkinson's Disease in Udon Thani Hospital, a Randomized Open-Label Comparison Trial

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Objective: Fludrocortisone is recommended for treatment of neurogenic orthostatic hypotension (nOH) in Parkinson's disease, but not yet approved by the Food and Drug Administration (FDA). The present study aimed to establish its efficacy compared with that of midodrine, the FDA-approved agent.

Materials and Methods: In these 12-week, open-label, non-inferiority trial, patients aged older than 18 with Parkinson's disease with nOH defined by a decrease of more than 20 mmHg systolic blood pressure (SBP) or more than 10 mmHg diastolic blood pressure (DBP) when measured in supine and 3-minute upright positions, were randomly assigned (1:1) to receive either fludrocortisone 0.1 mg daily in the morning or midodrine 5 mg twice a day in morning and noon. The primary outcome was the difference of SBP within a 3-minute upright position between the first and 12-week visits. The non-inferiority of fludrocortisone's efficacy was met if the lower limit of the one-sided 97.5% CI of the mean difference was not beyond -6 mmHg.

Results: Thirty-seven patients were enrolled, 18 with fludrocortisone and 19 with midodrine. Over the period of 12 weeks, the mean increase in SBP within a 3-minute upright position between the groups provided evidence of non-inferiority at 18.11±10.203 mmHg versus 17.36±9.662 mmHg, respectively, with a mean difference 0.74±3.266 (95% CI –5.887 to 7.372, p=0.02) for non-inferiority. The adverse events found more common in the fludrocortisone group were supine hypertension (SH) and hypokalemia.

Conclusion: Fludrocortisone raised SBP within a 3-minute upright position by the same amount as midodrine, despite having more adverse events.

Keywords: Orthostatic hypotension; Parkinson's disease; Fludrocortisone; Midodrine

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Clinical features of Parkinson's disease include motor and non-motor symptoms. Motor symptoms are often notable clinical manifestations, while non-motor symptoms are also common and disabling, but less recognized[1]. One of the most disabling non-motor symptoms is neurogenic orthostatic hypotension (nOH). Its prevalence in people with Parkinson's disease, as demonstrated in a meta-analysis, was 30.1%[2]. The nOH can increase the risk of fall and reduce patients' ability to perform their daily activities and decrease their well-being[3]. However, it is often inadequately treated[4]. The symptoms assessed by the Orthostatic Hypotension Questionnaire (OHQ) are composed of lightheadedness, dizziness, blurry vision, fatigue, impaired concentration, and head/neck discomfort[5]. The pathophysiology of nOH in Parkinson's disease patients was explained by the degeneration of post-ganglionic sympathetic neurons, which causes disorder of baroreflex function and reduces norepinephrine release[6]. The definition of orthostatic hypotension from the American Autonomic Society and the American Academy of Neurology (AAN) was a sustained reduction of systolic blood pressure (SBP) of 20 mmHg or more or diastolic blood pressure (DBP) of 10 mmHg or more within three minutes of active standing or head-up tilt to at least 60 degrees[7].

The management of nOH usually begins with

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non-pharmacological therapies such as increased water and salt intake, nighttime head tilt, stocking bandage, and leg crossing/squatting exercise. Overall, these strategies could increase SBP by 10 to 25 mmHg[8]. However, if they do not relieve the symptoms, the current pharmacological treatment for nOH, including with midodrine, fludrocortisone, pyridostigmine, and droxidopa, should be considered[9].

Midodrine is an alpha-1 adrenoceptor agonist. This medication converts to its active form, desglymidodrine, and increases vascular resistance, resulting in increased systolic and DBP. Midodrine was approved by the US-Food and Drug Administration (FDA) in 1996 for the treatment of orthostatic hypotension and dysautonomia[10]. The peak effect occurs in one hour and its effect duration lasts for two to four hours. The usual initial dose of midodrine is 2.5 mg, two to three times daily, and can be increased to 10 mg, two to three times daily[11]. The important adverse effects are supine hypertension (SH), defined as supine SBP of more than 140 mmHg or DBP of more than 90 mmHg, piloerection, and pruritus[11].

Fludrocortisone is a synthetic mineralocorticoid. It increases blood volume by acting as an aldosterone receptor agonist, which increases sodium reabsorption by the kidney and increases peripheral vascular resistance by sensitizing blood vessels to the effect of norepinephrine and angiotensin II[10]. The recommended dosages range between 0.1 to 0.3 mg daily, with the onset of action between three and seven days[12]. The common adverse effects are hypokalemia, SH, edema, and heart failure[12]. Guidelines advise using fludrocortisone as an off-label treatment for orthostatic hypotension even though it has not received US-FDA approval since its benefits outweigh its risks[8-10,13]. Some individuals in the clinical setting were unable to use midodrine due to its adverse effects, so fludrocortisone was prescribed instead. Therefore, the goal of this research was to directly compare fludrocortisone and midodrine's effects on patients with Parkinson's disease with nOH.

Materials and Methods

Study design

The present study was an open-label randomized trial designed to compare efficacy between fludrocortisone 0.1 mg/day and midodrine 10 mg/day. The hypothesis was that Parkinson's disease patients with orthostatic hypotension treated with fludrocortisone had an increased 3-minute upright BP similar to those treated with midodrine.

Study participants

Patients older than 18 were recruited from the neurology clinic of Udon Thani Hospital. They were eligible if they were diagnosed with Parkinson's disease according to the UK Brain Bank criteria and had not changed any medications, including Parkinson's drugs and antihypertensive agents, for at least four weeks before enrollment. Orthostatic hypotension was identified using the AAN criteria, which included a decrease in SBP or DBP of at least 20 mmHg or more in the supine position and at least 10 mmHg in the 3-minute upright position. Patients were considered symptomatic if they had lightheadedness and also experienced at least one of the following five orthostatic symptoms, dizziness, blurred vision, generalized weakness, fatigue, trouble with concentration, and head/neck discomfort. The exclusion criteria were condition of Parkinson-plus syndrome (PSP, MSA), other autonomic failure disorders, bed-ridden or wheelchair status, current use of MOAI agents, steroids, cigarettes or alcohol, any current treatment of orthostatic hypotension, and the presence of at least one comorbidity of cardiomyopathy, chronic lung disorder, cirrhosis, chronic kidney disease stage 5, and pregnancy.

Procedures

After providing written informed consent, all participants were 1:1 randomly assigned into each group to receive fludrocortisone or midodrine by computer. One labeled tablet of 0.1 mg Fludrocortisone was administered once a day in the morning. Two labeled tablets of 2.5 mg midodrine were taken twice a day in the morning and noon. At the first visit, collected data comprised of basic patient characteristics, duration of Parkinson's disease, modified Hoern and Yahr stage, and UPDRS-8. The following parameters were measured, complete blood count, blood urea nitrogen, creatinine, and electrolytes. All participants were scored for severity of lightheadedness from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst symptom or collapse. The questionnaires of Activities-specific Balance Confidence (ABC-16) (Thai version)[14], Parkinson's Disease Questionnaire (PDQ-8) (Thai version)[15], and EQ-5D-5L (Thai version) granted by EuroQol with No. 42111 were completed by participants. Blood pressure (BP) was measured by the automatic sphygmomanometer (DINAMAP DPC101X-EN). BP was measured after 10 minutes of resting in a supine position, then participants were asked to stand for three minutes, and BP values were

recorded while they remained in a standing position. Participants were informed about taking their regular breakfast and morning medication about one hour before the recording began.

Follow-up visits occurred at four and twelve weeks after the randomization. All participants were interviewed about the severity of lightheadedness from 0 to 10 and their self-answered questionnaires of ABC-16 (Thai version), EQ-5D-5L (Thai version), and PDQ-8 (Thai version). Medication compliance was calculated as the percentage of tablets that they took divided by the tablets that were prescribed. BP was measured by the same procedure as on the first visit. The 12-week follow-up visit included tests for complete blood count, blood urea nitrogen, creatinine, and electrolyte. Adverse events were monitored.

BP measurement and all questionnaire interviews were performed by neurologic nurses unaware of the treatment assignments.

Outcomes

The primary outcome was the change of SBP within a 3-minute upright position between the first visit and the 12-week follow-up visit. The secondary outcomes included the change of 3-minute upright DBP between the first visit and the last visit, the change of the lightheadedness score between the first visit and the last visit, the number of participants who were not compatible with orthostatic hypotension criteria, and the average percentage of confidence of balance measured by ABC-16 at the last visit. The quality of life was measured by two questionnaires. First was the PDQ-8 (Thai version) with Cronbach's alpha coefficient=0.92, which had eight questions. Each question represented each specific situation had five answers with a score of 0 to 4, with 0 indicating an event never occurred and 4 indicating an event always occurred[16]. Second, the EQ-5D-5L (Thai version) was calculated into the EQ-5D-5L utility score from 0 to 1. Zero represented the bad quality of life as a near-dead condition, and 1 represented the best health quality. However, a utility score could show a minus number that meant health quality was worse than death[17]. The safety outcome was any adverse effect of medication such as SH, tingling sensation, hypokalemia, and other serious events such as death, seizure, or hospitalization.

Statistical analysis

The N4Studies application was used for calculating the sample size, and Stata/SE version 17 was used for all analyses. The number of samples was calculated by the non-inferiority two-sample trial formula for continuous data[18]. Because there is no previous study that directly compared the effects of fludrocortisone and midodrine, the authors calculated the difference in mean SBP from the study of each agent. Midodrine can raise SBP by about 21 mmHg[19], and fludrocortisone can raise SBP by about 9 mmHg[20]. To satisfy the non-inferiority hypothesis with a power of 80%, the authors set the lower boundary of the one-sided 97.5% confidence interval as needed at -6 mmHg. This value was derived from about 50% of the mean SBP difference between an outcome with fludrocortisone as compared with midodrine. The ratio between the two groups was 1:1, so the sample size was 18 for each group.

Patients' characteristics were calculated by descriptive statistics. The primary analysis was designed to determine whether the effect of fludrocortisone to raise SBP within a 3-minute position was non-inferior to the effect of midodrine as evaluated with the use of an independent sample t-test. The secondary outcomes were analyzed by an independent sample t-test for continuous outcomes and a chi-square test for categorical data. The Mann-Whitney U test was used instead if any continuous data were not assumed to be of normal distribution. All analyses were based on the intention-to-treat principle, and a p-value less than 0.05 represented the statistical significance.

The protocol and consent forms were approved by the Human Subjects Ethics and Research Committee of Udon Thani Hospital, EC no. I084/2563. There was no commercial fund support, and the authors declared no conflict of interest.

Results

The research was conducted between March and November 2021, and 40 patients were recruited. Three subjects withdrew before allocation. Thirty-seven subjects with a mean age of 65.92 years, including 21 males and 16 females, were randomized into two groups with 18 participants in the fludrocortisone arm and 19 participants in the midodrine arm. Data sets were included if trial arms were completed. As shown in Table 1, the clinical characteristics of both groups were well matched. At the final visit, each arm's adherence to allocated treatment was high with 94.05±4.872% for the fludrocortisone arm and 92.27±5.603% for midodrine arm (p=0.31). No participants discontinued therapy before the final visit.

The primary outcome is demonstrated in Figure 1. The increase in SBP values of 3-minute

Table 1. Patients' baseline characteristic

Variables	Fludrocortisone (n=18)	Midodrine (n=19)	p-value
Sex: male; n (%)	10 (55.56)	11 (57.89)	0.909
Early-onset PD; n (%)	5 (27.78)	3 (15.79)	0.376
H&Y stage; n (%)			
1.5	1 (5.56)	0 (0.00)	
2	0 (0.00)	1 (5.26)	
2.5	0 (0.00)	2 (10.53)	
3	3 (16.67)	5 (26.32)	
4	14 (77.78)	11 (57.89)	0.186
Diabetes mellitus; n (%)	2 (11.11)	3 (15.79)	0.677
Ischemic heart disease; n (%)	1 (5.56)	1 (5.26)	0.969
Hypertension; n (%)	7 (38.89)	4 (21.05)	0.235
Old stroke; n (%)	4 (22.22)	1 (5.26)	0.132
Benign prostate hyperplasia; n (%)	2 (11.11)	1 (5.26)	0.515
Chronic kidney disease stage 3 or 4; n (%)	1 (5.56)	1 (5.26)	0.969
Dementia; n (%)	3 (16.67)	4 (21.05)	0.734
Supine hypertension; n (%)	3 (16.67)	5 (26.32)	0.476
Dopamine agonist; n (%)	13 (72.22)	11 (57.89)	0.495
Prameplexole	7 (38.89)	6 (31.58)	0.737
Ropinirole	6 (33.33)	5 (26.32)	0.721
Alpha blocker; n (%)	2 (11.11)	1 (5.26)	0.515
Other antihypertensive agent; n (%)	6 (33.33)	4 (21.05)	0.401
Age (years); mean±SD	63.61±9.4	68.11±8.2	0.386
Duration of PD (years); mean±SD	7.11±3.954	6.84±3.862	0.821
L-DOPA (mg/day); mean±SD	497.20±163.1	489.80±148.9	0.481
Entacarpone (mg/day); mean±SD	640.00±206.6	557.10±181.3	0.406
Dopamine agonist (mg/day); mean±SD			
Prameplexole	1.13±0.3	0.94±0.5	0.434
Ropinirole	6.67±1.6	5.67±1.9	0.361
Systolic BP (mmHg); mean±SD			
Supine position	126.61±15.5	132.79±11.6	0.176
3-minute upright position	97.50±17.1	103.05±13.4	0.278
Δ BP supine and 3-min	29.11±10.8	29.73±9.1	0.850
Diastolic BP (mmHg); mean±SD			
Supine position	75.17±9.9	75.21±9.9	0.989
3-minute upright position	63.33±11.6	67.58±13.5	0.313
Δ BP supine and 3-min	11.83±8.2	7.63±11.7	0.217
Lightheadedness severity score; mean±SD	7.61±1.2	8.00±1.1	0.311
Average ABC-16 score (%); mean±SD	49.78±21.6	51.09±23.9	0.863
PDQ-8 sum score; mean±SD	11.78±0.5	8.63±5.7	0.086
EQ-5D-5L utility score; mean±SD	0.514±0.24	0.563±0.33	0.610
Hemoglobin (gm/dL); mean±SD	12.3±1.6	12.5±1.6	0.887
Blood urea nitrogen (mg/dL); mean±SD	13.8±6.7	15.3±4.0	0.401
Creatinine (mg/dL); mean±SD	0.8±0.3	1.0±0.3	0.139
Sodium (mmol/L); mean±SD	138.7±3.2	138.8±2.6	0.856
Potassium (mmol/L); mean±SD	3.9±0.3	3.9±0.5	0.763

BP=blood pressure; Δ BP supine and 3-min=the difference of BP values between supine position and 3-minute upright position; ABC-16=activities-specific balance confidence-16; PDQ-8=Parkinson's Disease Questionnaire-8; SD=standard deviation

Table 2. Secondary outcome

Variables	Fludrocortisone (18) mean±SD	Midodrine (19) mean±SD	95% CI	p-value
Outcome at the final visit				
Systolic BP (mmHg)				
• Supine position	140.83±14.6	133.84±10.8	–1.552 to 15.534	0.106
• 3-minute upright position	115.61±17.0	120.42±10.0	–14.082 to 4.462	0.301
• Δ BP Supine and 3-min	25.22±16.0	13.42±10.1	2.915 to 20.686	0.011
Diastolic BP (mmHg)				
• Supine position	79.67±8.9	74.89±9.7	–1.459 to 11.003	0.129
• 3-minute upright position	69.39±10.3	69.89±9.3	–7.039 to 6.027	0.876
• Δ BP Supine and 3-min	10.28±8.9	5.00±9.0	–0.733 to 11.288	0.083
Lightheadedness severity score	6.06±1.7	4.21±1.6	0.716 to 2.974	0.002
ABC16 average (%)	49.69±21.4	55.17±24.6	–20.915 to 9.965	0.476
PDQ-8 sum score	11.50±6.2	8.68±5.3	–1.036 to 6.668	0.147
EQ-5D-5L utility score	0.474±0.27	0.628±0.29	–0.343 to 0.034	0.105
Potassium (mmol/L)	3.7±0.4	4.0±0.5	–0.536 to 0.210	0.069
The difference in outcome between the first and final visit				
Systolic BP (mmHg)				
• Supine position	14.22±14.2	1.05±9.8	5.076 to 21.263	0.002
• 3-minute upright position	18.00±10.2	17.37±9.7	–5.887 to 7.372	0.301
Diastolic BP (mmHg)				
• Supine position	4.50±12.38	–0.32±12.1	–3.367 to 12.999	0.240
• 3-minute upright position	6.05±11.8	2.31±14.06	–4.959 to 12.439	0.389
Lightheadedness severity score	1.55±1.9	3.79±1.5	–3.383 to –1.085	0.001
ABC16 average (%)	–0.91±18.8	4.08±6.2	–15.264 to 6.922	0.450
PDQ-8 sum score	–0.28±6.6	0.53±4.65	–4.139 to 3.478	0.861
EQ-5D-5L utility score	–0.394±0.26	0.656±0.32	–0.299 to 0.895	0.280

BP=blood pressure; Δ BP Supine and 3-min=the difference of BP values between supine position and 3-minute upright position; ABC-16=Activities-specific Balance Confidence-16; PDQ-8=Parkinson's Disease Questionnaire-8; SD=standard deviation

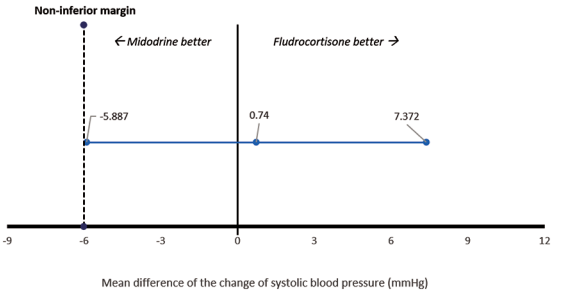

Figure 1. Primary outcome: the mean difference in the change of SBP within 3 minutes of the standing posture comparison between groups.

Remark: The figure displayed the 95% confidence interval for the mean difference (mf) of the change in SBP within 3 minutes of the upright position between the first visit and the final visit for the fludrocortisone group compared to the midodrine group. The lower margin of mf (–5.887) was not beyond the non-inferior margin (–6 mmHg). This indicated that fludrocortisone increased SBP in a 3-minute standing posture non-inferior to midodrine.

upright position in the fludrocortisone group compared to that in the midodrine group between the first visit and the final visit provided evidence of non-inferiority with the mean change of SBP at 18.11±10.2 mmHg and 17.36±9.7 mmHg, respectively, and the mean difference at 0.74±3.3 (95% CI –5.887 to 7.372, p=0.023) for non-inferiority.

In the final visit, the decrement of SBP between supine position and after 3-minute standing position in fludrocortisone group was significantly larger when compared with midodrine group as showed in Table 2. Furthermore, seven participants receiving fludrocortisone and twelve receiving midodrine were no longer compatible with the AAN definition of orthostatic hypotension (OR 2.694, 95% CI 0.713 to 10.178, p=0.133). This would indicate that midodrine tended to improve orthostatic hypotension more than the other drug. Other BP parameters and laboratory results did not reveal any significant difference between the groups.

The main orthostatic hypotension symptom in the present study was lightheadedness, as demonstrated

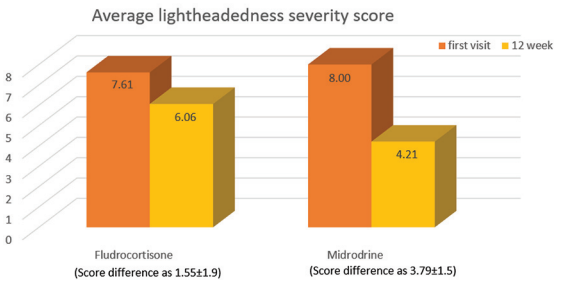

Figure 2. Average lightheadedness severity score.

Remark: At the 12-week visit, fludrocortisone's average lightheadedness severity score was significantly higher than midodrine's (6.06±1.7 and 4.21±1.6, respectively, p=0.002), and its decrease in score was less than the other agent's (change of score –1.55±1.947 and –3.79±1.475 respectively, mean difference –2.23±0.566, 95% CI –3.383 to –1.085, p=0.01).

Table 3. Adverse events

Adverse effects	Fludrocortisone (n=18); n (%)	Midodrine (n=19); n (%)
Supine Hypertension	10 (55.56)	4 (21.05)
Hypokalemia	6 (33.33)	2 (10.53)
Leg edema	4 (22.22)	1 (5.26)
Nausea	3 (16.67)	1 (5.26)
Palpitation	2 (11.11)	2 (10.53)
Urinary retention	1 (5.56)	2 (10.53)
Paresthesia	1 (5.56)	4 (21.05)
Pruritus	1 (5.56)	2 (10.53)
Piloerection	1 (5.56)	3 (15.79)

in Figure 2. Participants in both groups experienced the same level of lightheadedness severity at the first visit with 7.61±1.2 and 8.00±1.1, respectively (p=0.311), but at the final visit, the fludrocortisone group decreased in severity score was less than the midodrine group with a change of score at 1.55±1.9 and 3.79±1.5 respectively, and a mean difference at –2.23±0.6 (95% CI –3.383 to –1.085, p=0.001). This indicated that participants treated with midodrine experienced greater improvements in their orthostatic hypotension symptoms than those treated with fludrocortisone. However, at the final visit, there was no difference between the two groups in the confidence of balance measured by ABC-16 or their quality of life as judged by either the PDQ-8 or EQ-5D-5L utility score, as shown in Table 2. Additionally, there was no difference between the first and final visits in the score change determined by three questionnaires, as demonstrated in Table 2.

The important adverse effect was SH. SBP in the supine position increased more in the fludrocortisone group than in the midodrine group when comparing the changes between the first and the final visit at 14.22±14.2 and 1.05±9.8 mmHg, respectively (95% CI 5.076 to 21.263, p=0.002), as demonstrated in Table 3. Furthermore, at the final visit, participants receiving fludrocortisone were much more compatible with the SH criteria than those receiving midodrine with 10 and 4 participants, respectively (OR 4.69, 95% CI 1.108 to 19.834 p=0.031). Another notable adverse effect was hypokalemia, defined as serum potassium below 3.5 mmol/L. Participants in the fludrocortisone group at the final visit frequently reported this without experiencing any other symptoms like weakness or arrhythmia with six and two participants (OR 4.25, 95% CI 0.729 to 24.769, p=0.092). On the other hand, the group receiving midodrine frequently had paresthesia with one and four participants (OR 0.22, 95% CI 0.022 to 2.197, p=0.340). Other adverse effects did not show any significant difference between the groups, as shown in Table 3. No serious adverse events happened in the present research.

Discussion

The present study is the first study to directly compare the effects of fludrocortisone, an off-label medication, and midodrine, an FDA-approved medication, in Parkinson's disease patients with nOH. The results demonstrated that both agents raised SBP during a 3-minute upright position after the 12-week treatment despite each agent's different mechanisms. The mean elevated SBP value in the midodrine group was consistent with earlier research, whereas that in the fludrocortisone group was greater than the previous studies[19,20].

Interestingly, the fludrocortisone group's SBP difference between supine and after 3-minute upright position was greater when compared to the midodrine group at the final visit. The reason was that fludrocortisone could raise SBP in both the supine and upright positions, whereas midodrine raised SBP in the upright position more than in the supine. These finding had two consequences. First, fewer participants receiving fludrocortisone than those receiving midodrine could recover from orthostatic hypotension, according to the AAN criteria. Second, more fludrocortisone-treated participants developed SH. The various pharmacodynamics of each agent may provide an explanation for the postulated mechanism. Fludrocortisone influenced intravascular volume status equivalent in supine and upright posture, whereas midodrine had an effect on reflex vasoconstriction greater in upright posture than in

supine position[10]. Another explanation for this finding was that the present study was designed to measure blood pressure only in the morning. Therefore, participants receiving fludrocortisone, which had a duration of about 24 hours, might experience the cumulative effect of the previous doses. In contrast to those receiving midodrine, which has a two-to-six-hour duration and was administered only in the morning and noon, the subjects only experienced the effect of the morning dose[11].

The previous Thai research indicated that lightheadedness was the most significant symptom among patients with orthostatic hypotension[21]. Therefore, lightheadedness was selected as the main symptom in the present investigation. The present study participants had a higher baseline score for lightheadedness than those in the previous study at 7.61±1.2 for fludrocortisone, and 8.00±1.1 for midodrine versus 3.67±2.54 for the previous research[21]. Another aspect that previous research and the present study observed was the ability to balance, evaluated by ABC-16. The present study participants had a lower average baseline composite score of ABC-16 than those in the previous study at 49.78±21.6 for fludrocortisone, and 51.09±23.9 for midodrine versus 67.4±25.9 for the previous research[21]. This could be explained by the fact that most subjects in the previous study were classified as H&Y stages 2.5 and 3[21], whereas almost all subjects in the present study were classified as H&Y stages 3 and 4. After 12 weeks of treatment, subjects receiving midodrine significantly improved the lightheadedness score more than those receiving fludrocortisone, however there was no difference in the effect of balance measured by ABC-16. This result may be due to the medication's effect on the reduced variation of SBP between supine and 3-minute upright position[9]. Unfortunately, the design of the present study was insufficient to conclusively demonstrate the correlation between SBP and lightheadedness.

The Thai Parkinson's patients' quality of life was assessed using the PDQ-8 and EQ-5D-5L. The average PDQ-8 score was 12.25±7.19(15), while the average EQ-5D-5L utility score was 0.481±0.330[22]. At the baseline of the present study, the scores determined by each questionnaire were consistent with the earlier references. After 12 weeks of treatment, there was no significant improvement although average EQ-5D-5L utility score of participants receiving midodrine tended to be better. There are two reasons for this. First, motor symptoms of Parkinson's disease had more impact on the quality of life. Second, the study's duration was insufficient to reveal any change.

SH, as mentioned earlier, was the only adverse event noticed to be significantly different between the two groups in the present investigation. The other adverse events were the same as those in the previous research for each medicine with no significant difference between the groups[11,19,20]. The hypokalemia was found more frequently in the fludrocortisone arm. This can be explained directly by its pharmacodynamic mechanism[10,11], as can the scalp paresthesia and piloerection observed in the midodrine arm by its action to alpha-adrenergic agonist effects on skin and skin appendages[10,11].

The results of the present study were not exactly consistent with the recent meta-analysis of each agent. According to a Cochrane database systematic review, fludrocortisone's effect on blood pressure, orthostatic symptoms, or adverse events in people with diabetes or Parkinson's disease who had orthostatic hypotension was unclear[23]. Similarly, the meta-analysis of midodrine for orthostatic hypotension concluded that it may improve standing SBP but has no benefit on supine to standing SBP but increases the risk of side effects[19]. The explanation could be that first, the present study subjects were restricted to Parkinson's disease and not to any other causes of orthostatic hypotension. Second, the doses and administration methods of each agent used in the present research differed from those of the previous studies[19,23], which almost all used maximum doses. Therefore, some dose-dependent effects, such as SH in midodrine or time-dependent effects such as cardiac hypertrophy or heart failure in fludrocortisone, might be undiscovered.

The present study had limitations. 1) The open-labeled design introduced bias. 2) Factors, such as daily salt and water intake, were not controlled and might affect BP values. 3) Patients with Parkinson's disease in H & Y stage 5, which was strongly associated with orthostatic hypotension, were excluded because of their difficulty standing. 4) The present study's definition of symptomatic orthostatic hypotension may have led to overlook patients with other orthostatic hypotension symptoms without lightheadedness. And 5) because nOH is a chronic condition, the study's duration was insufficient to reveal the long-term effects and complications.

Conclusion

After 12 weeks of treatment for symptomatic orthostatic hypotension in Parkinson's disease, fludrocortisone, compared to midodrine, increased the

SBP within a 3-minute standing position and provided evidence of non-inferiority. However, the midodrine significantly improved the lightheadedness severity score and caused fewer adverse effects on SH and hypokalemia.

What is already known on this topic?

From the current ACC guidelines, fludrocortisone can be used as an off-label medication for the treatment of orthostatic hypotension with an IIa recommendation. A new Cochrane systematic review published in May 2021, found very low certainty evidence about its effects on both BP and symptoms.

What this study adds?

This study demonstrated the efficacy of fludrocortisone for the treatment of orthostatic hypotension in Parkinson's disease, so the authors recommend it as an alternative medication to midodrine. Moreover, this finding may improve the quality of evidence needed to officially approve fludrocortisone for the treatment of this condition.

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Conflicts of interest

The authors declare no conflict of interest.

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