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Effects of the rotigotine transdermal patch versus oral levodopa on swallowing in patients with Parkinson's disease

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ABSTRACT

Objectives: Abnormal swallowing or dysphagia is a potentially fatal symptom in Parkinson's disease (PD) and is characterized by frequent silent aspiration, which is an unrecognized risk for aspiration pneumonia. While the effects of oral levodopa on swallowing functions remain controversial, several small-scale studies have reported that rotigotine transdermal patch seems effective. The different effects between levodopa and rotigotine may be attributed to continuous dopaminergic stimulation (CDS), however, the absence of direct comparative evidence precludes conclusion.

Methods: In the present retrospective open-label study of 50 patients with PD, swallowing functions were assessed via videofluoroscopic (VF) examination before and after treatment. Treatment included 2 mg/day rotigotine transdermal patch ($N = 29$) or 200 mg/day oral levodopa with carbidopa ($N = 21$) in drug-naïve and add-on groups of patients.

Results: Rotigotine more consistently improved all measures assessed via VF examination. Such effects were similar to those in the drug-naïve and add-on groups. Improvement and responder rates of certain measures were significantly higher in the rotigotine group than in the levodopa group.

Conclusions: Our finding that rotigotine (levodopa equivalent dose = 60 mg) was more consistently effective than 200 mg/day oral levodopa suggests that CDS is more important in improving swallowing functions.

1. Introduction

Abnormal swallowing or dysphagia is a potentially fatal symptom in Parkinson's disease (PD), as well as other neurodegenerative diseases [1–3]. Dysphagia is characterized by frequent silent aspiration, an unrecognized risk for aspiration pneumonia [4]. The effects of levodopa on swallowing remain controversial as the results of a recent meta-analysis study denied its effect [5]. However, the study only collected data from 5 reported studies with various patient backgrounds (Table S1), whose duration of the disease ranged 3.2–11 years [6–10]. A more recent study demonstrated the effectiveness of levodopa on swallowing [11]. In contrast to levodopa, several studies have reported that the dopamine agonists apomorphine and rotigotine alleviated dysphagia in some patients with PD [7,12–14] and improved pharyngeal transit durations (PTDs, also called pharyngeal transit times [PTTs]) [12,13]. Unfortunately, the number of the reported patients for swallowing was very small, < 10 patients for rotigotine. Because rotigotine transdermal patch but not oral levodopa successfully achieves continuous dopaminergic stimulation (CDS), their different effects on swallowing may be attributed to CDS. However, the absence of direct comparative evidence precludes conclusion. In this present open-label retrospective study, we aimed to compare the effectiveness of levodopa and rotigotine on swallowing by videofluoroscopic (VF) examination with evaluators blinded to all clinical details in patients with PD.

2. Patients and methods

2.1. Patients

Patient demographics are summarized in Table 1. In this study, levodopa was always administered in combination with carbidopa (10 mg carbidopa per 100 mg levodopa). We retrospectively examined 50

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Table 1
Demographics of patients with Parkinson's disease in this study.

Group	Levodopa-initiated	Rotigotine-initiated	Levodopa-add-on	Rotigotine-add-on
Patient number	15	15	6	14
Sex	M8, F7	M6, F9	M4, F2	M7, F7
Age of examination (yr)	73 ± 7	76 ± 4	80 ± 5	80 ± 6
Age of onset (yr)	71 ± 6	73 ± 4	76 ± 4	76 ± 5
Hoehn-Yahr	2.8 ± 0.4	3.0 ± 0.5	3.2 ± 0.4	3.0 ± 0
UPDRS III	23 ± 6	24 ± 11	25 ± 6	21 ± 6
LED (mg/day)	0	0	160 ± 31	334 ± 53[a]

UPDRS III, Unified Parkinson's Disease Rating Scale part III; LED, levodopa equivalent dose.
[a] The LED in the rotigotine group was larger than that in the levodopa group (Mann-Whitney U test, $p < 0.01$).

consecutive patients with PD who underwent VF examinations before and after treatment from 2014 to 2018. Patients did not have prominent autonomic dysfunction, apparent dementia, signs of upper motor neuron disease, painful or debilitating disorders, or previous history of stroke. The body weight was 55.7 ± 10.0 kg (mean ± SD) in the levodopa group and 53.0 ± 9.0 kg in the rotigotine group. Fifteen drug-naïve patients with PD (8 men and 7 women, age 73.0 ± 6.7 years, mean ± SD) initially received oral levodopa (200 mg/day levodopa, taken in divided doses twice daily [morning and evening]). Fifteen drug-naïve patients with PD (6 men and 9 women, age 75.5 ± 4.1 years) initially received a rotigotine transdermal patch (2 mg/day rotigotine [the patch contains 4.5 mg rotigotine, but only 2 mg/day is absorbed]).

Similarly, we examined 6 patients with PD (4 men and 2 women, age 80.0 ± 4.7 years) who additionally received 200 mg/day levodopa during the treatment with the rotigotine transdermal patch. Patients received 4–6 mg/day rotigotine [levodopa equivalent dose [LED] = 160 ± 31 mg/day] [15]. Fourteen patients with PD (7 men and 7 women, age 79.6 ± 6.2 years) additionally received a 2-mg/day rotigotine transdermal patch during treatment with other PD medicines, including oral levodopa. Patients received levodopa with or without other anti-PD medication (LED = 334 ± 53 mg/day), such as pramipexol (0.5 mg/day, $n = 1$) and entacapone (100–300 mg/day, $n = 5$). During the study period, we found that only one patient was treated with a higher dose of rotigotine and underwent VF examination before and after treatment. This patient was excluded from the current study because of inadequate data for statistical analyses. The parameters before treatment did not differ between the levodopa and rotigotine groups, except for LED. All patients were clinically diagnosed as having PD by board-certified neurologists in accordance with the UK Parkinson's disease Society Brain Bank Clinical Diagnostic Criteria. This study was approved by our Institutional Review Board. Our cohort included only two patients who had a history of aspiration pneumonia before this study (one among the drug-naïve patients on rotigotine treatment and the other in the rotigotine add-on group).

2.2. VF examinations

VF examination was performed according to a previously described method, with a slight modification [16,17]. Briefly, a diluted solution of barium (5 ml) was swallowed twice. If the swallowing problem was not very severe, as indicated by the procedure and rating scales described below, a concentrated barium solution was then swallowed once. The amount was not restricted, and the subject was requested to swallow as usual to detect swallowing problems encountered in daily life. Worse scores were obtained on each swallow according to the scales described below. Six grams of barium mixed with jelly was then swallowed. The results of VF examination were evaluated according to a Japanese scale established by the Japanese Society of Dysphagia Rehabilitation, which is already reported several times in the English-language literature (please see Table S2), as well as according to the Dysphagia Outcome and Severity Scale (DOSS) [2,3,17]. The following VF variables were assessed according to the Japanese scale: lip closure, bolus formation, bolus transport during the oral phase, constriction of the pharynx, elevation of the larynx, bolus stasis at the valleculae and pyriform sinus, and aspiration during the pharyngeal phase. A three-point scale was used to semi-quantify each variable in a series of VF examinations: 3 (normal), 2 (disturbed), and 1 (severely disturbed). When the Japanese scale was used, the oral phase (3 = severely affected and 9 = normal) and the pharyngeal phase (4 = severely affected and 12 = normal) were separately evaluated, and the values were summed to derive the total score. The DOSS (1 = severely affected and 7 = normal) is more widely used internationally, but the oral and pharyngeal phases cannot be separately evaluated. Penetration-Aspiration scale (PAS) is an 8 point-scale (1 = no penetration and 8 = aspiration with no ejection efforts) [18]. One speech language pathologist and one neurologist, who were blinded to all clinical details, independently scored the results for each patient. Both had > 10 years of experience in swallowing evaluation. > 90% of the point scores were matched between the initial evaluators. If there was any discrepancy, 3 additional neurologists who were also experts in swallowing evaluation and disorders decided which score was appropriate.

PTD was calculated from the time of arrival of the bolus head (5 ml of barium) at the ramus of the mandible until the time that the tail of the bolus passed through the upper esophageal sphincter, as described previously [12]. The institutional normal range of PTD (mean ± 2 SD) was obtained from 8 healthy controls (age 64 ± 21 years).

All patients were evaluated before and 1 to 3 weeks after starting initial or add-on treatment. When patients received levodopa, VF examination was performed 2–3 h after the last dose of levodopa, during the on-state. Although our patients did not exhibit marked inter-daily or intra-daily variations of symptoms, we did not conclude whether the examinations were performed in the best-on state.

2.3. Evaluation of parkinsonism

Parkinsonism was evaluated according to the Hoehn-Yahr stage and the United Parkinson's Disease Rating Scale (UPDRS), Part III (UPDRS-III, motor examination). When patients received levodopa, UPDRS was assessed 2–3 h after the last dose of levodopa. Our cohort included only 5 patients with Hoehn-Yahr stage II (2 in the rotigotine group and 3 in the levodopa group) and 3 with Hoehn-Yahr stage IV (2 in the rotigotine group and 1 in the levodopa group). The numbers were not enough to perform statistical analyses by dividing groups with different stages.

2.4. Statistical analyses

The aforementioned scores and times were compared between pre- and post-treatment. We chose the Wilcoxon (paired) signed-rank test, because the data were nonparametric or non-normally distributed. The responder rate was compared between the treatment groups using the Fisher's exact test, since the chi-square test was not appropriate for small sample sizes. Improvements of aforementioned scores and times was compared between the treatment groups using the Mann-Whitney U test. The improvements of scores during the oral phase, and during pharyngeal phase, and total scores, and DOSS were defined as post-treatment scores minus pre-treatment scores, since higher scores were associated with better functions. The improvements of PTD, PAS, and UPDRS-III were defined as pre-treatment values minus post-treatment values, since higher values were associated with worse functions. The improved ratios (improvements of PTD, PAS, or UPDRS-III divided by pre-treatment values) were also compared using the Mann-Whitney U test. Statistical analyses were performed with SPSS software version 22. We considered $p < 0.05$ to be significant.

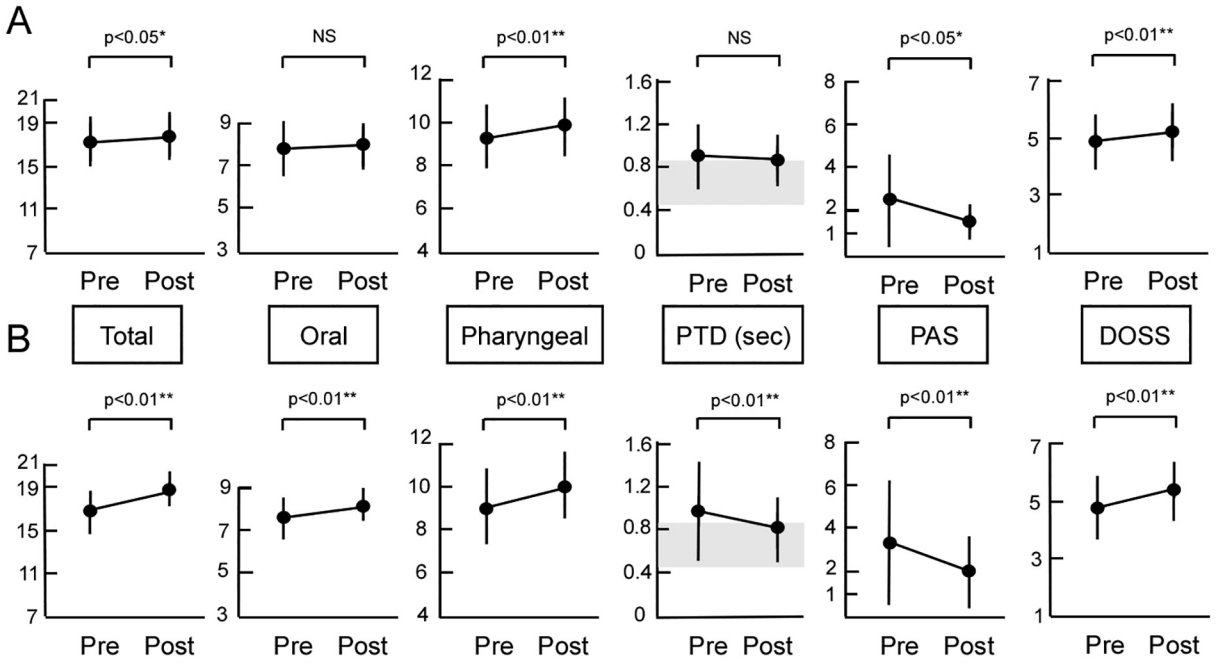

Fig. 1. Swallowing function in 50 patients with Parkinson's disease before (pre) and after (post) application of an oral levodopa (A, $N = 21$) or a rotigotine transdermal patch (B, $N = 29$). Videofluoroscopic (VF) examinations revealed significant improvements (Wilcoxon signed-rank test) in total scores, scores during the pharyngeal phase, Penetration-Aspiration scale (PAS) scores, and the Dysphagia Outcome and Severity Scale (DOSS) scores in the levodopa group ($p < 0.05$* or $p < 0.01$**), but in all measures, including scores during the oral phase and pharyngeal transit duration (PTD), in the rotigotine group (p < 0.01**). The shaded area in PTD indicates the normal range.

3. Results

3.1. Improvement in swallowing function in the 50 patients after treatment

Pharyngeal scores and total scores on the Japanese scale, PAS, and DOSS on VF examinations improved in patients treated with levodopa ($N = 21$, p < 0.05 or $p < 0.01$, Wilcoxon rank test, Fig. 1A). In contrast, oral scores and PTD did not change. All measures on VF examinations improved significantly in patients treated with rotigotine ($N = 29$, $p < 0.01$, Wilcoxon rank test, Fig. 1B).

3.2. Improvement in swallowing function in 30 drug-naïve patients after treatment

Pharyngeal scores and total scores on the Japanese scale, PAS, and DOSS on VF examinations improved in patients treated with levodopa ($N = 15$, $p < 0.05$ or $p < 0.01$, Wilcoxon rank test, Fig. 2A). In contrast, oral scores and PTD did not change. All measures on VF examinations improved significantly in patients treated with rotigotine (N = 15, p < 0.01, Wilcoxon rank test, Fig. 2B).

3.3. Improvement in swallowing function in 20 patients after additional treatment (add-on)

No measures on VF examinations significantly improved in patients treated additionally with levodopa ($N = 6$, Wilcoxon rank test, Fig. 3A). All measures, except the PAS score, improved significantly in patients treated additionally with rotigotine ($N = 14$, $p < 0.05$, Wilcoxon rank test, Fig. 3B).

3.4. The results of comparison between the treatment groups

Improvements of oral phase scores and total scores on VF examinations in total patients with rotigotine treatment were significantly higher than in total patients with levodopa treatment (Fig. 4A). Other measures did not significantly differ between groups. Improvements of oral phase scores and total scores, and improved ratios of PTD in patients initially treated with rotigotine were significantly higher than those with levodopa (Fig. 4B).

3.5. Responder rates of rotigotine and levodopa

Responder rates of oral phase scores and PTD in the 50 patients were significantly higher in the rotigotine group than in the levodopa group ($p < 0.05$ or $p < 0.01$, Fisher's exact test, Table 2). The same result was obtained in drug-naïve patients. In the add-on treatment study, no difference was observed.

3.6. Improvements in parkinsonism as evaluated by the Hoehn-Yahr stage and UPDRS-III

Parkinsonism improved in all patients according to the UPDRS-III score, with no significant change in the Hoehn-Yahr stage. The improvement or improved ratios did not significantly differ between the treatment groups.

4. Discussion

Our open-label study on drug-naïve and add-on-treated patients with PD showed that all measures of swallowing functions on VF evaluations were significantly improved by application of a rotigotine transdermal patch. In addition to the improvement during the oral phase, which is associated with voluntary movement, rotigotine improved the scores during the pharyngeal phase, which is associated mainly with involuntary sequential reflexes of striatal muscles, suggesting that central dopaminergic stimulation facilitates both the oral and pharyngeal phases. In contrast, the oral phase score and PTD were not significantly improved by oral levodopa, partly because the responder rates of these measures were significantly smaller in the levodopa group. The comparison between the treatment groups revealed

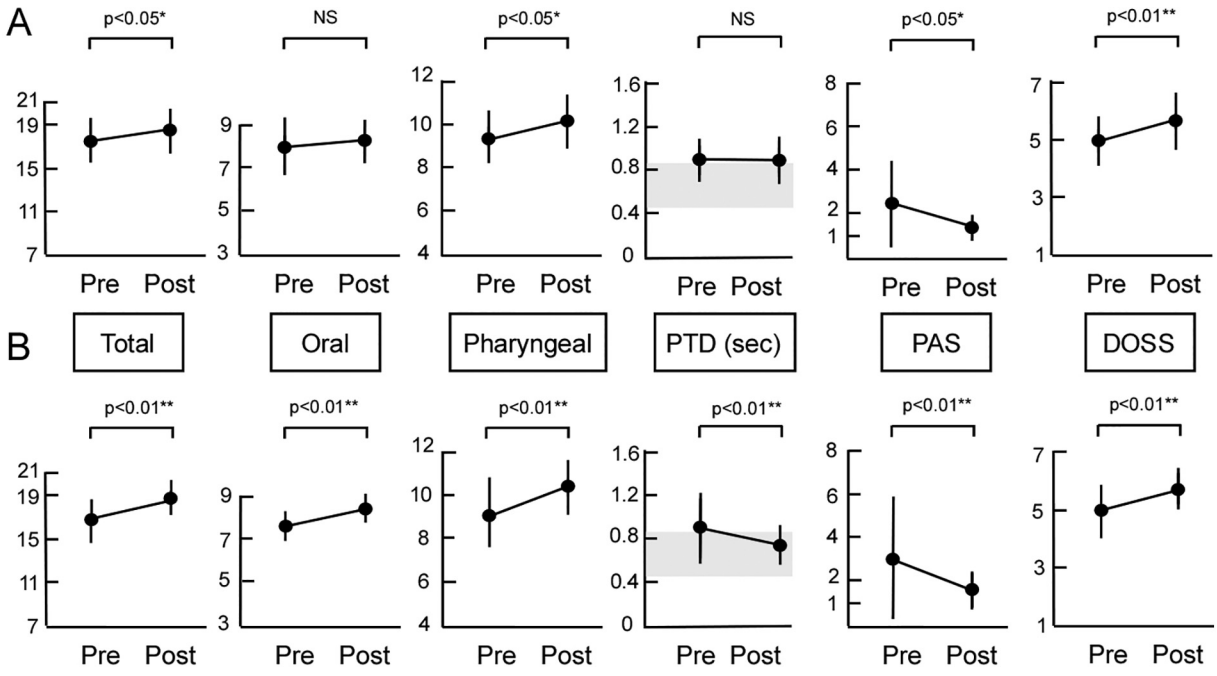

Fig. 2. Swallowing function in 30 drug-naïve patients with Parkinson's disease before (pre) and after (post) application of an oral levodopa (A, $N = 15$) or a rotigotine transdermal patch (B, N = 15). Videofluoroscopic (VF) examinations revealed significant improvements (Wilcoxon signed-rank test) in total scores, scores during the pharyngeal phase, Penetration-Aspiration scale (PAS) scores, and the Dysphagia Outcome and Severity Scale (DOSS) scores in the levodopa group ($p < 0.05$* or p < 0.01**), but in all measures, including scores during the oral phase and pharyngeal transit duration (PTD), in the rotigotine group ($p < 0.05$* or p < 0.01**). The shaded area in PTD indicates the normal range.

that rotigotine was more effective than levodopa in improvements of oral phase scores and total scores. Because the specific affinities of dopamine receptor subtypes for rotigotine are similar to those for dopamine derived from levodopa as described below [19], and because 2 mg/day rotigotine (LED = 60 mg) was more consistently effective than 200 mg/day oral levodopa, we speculate that CDS is more important in improving swallowing functions.

The inconsistent responsiveness of levodopa agrees with the results

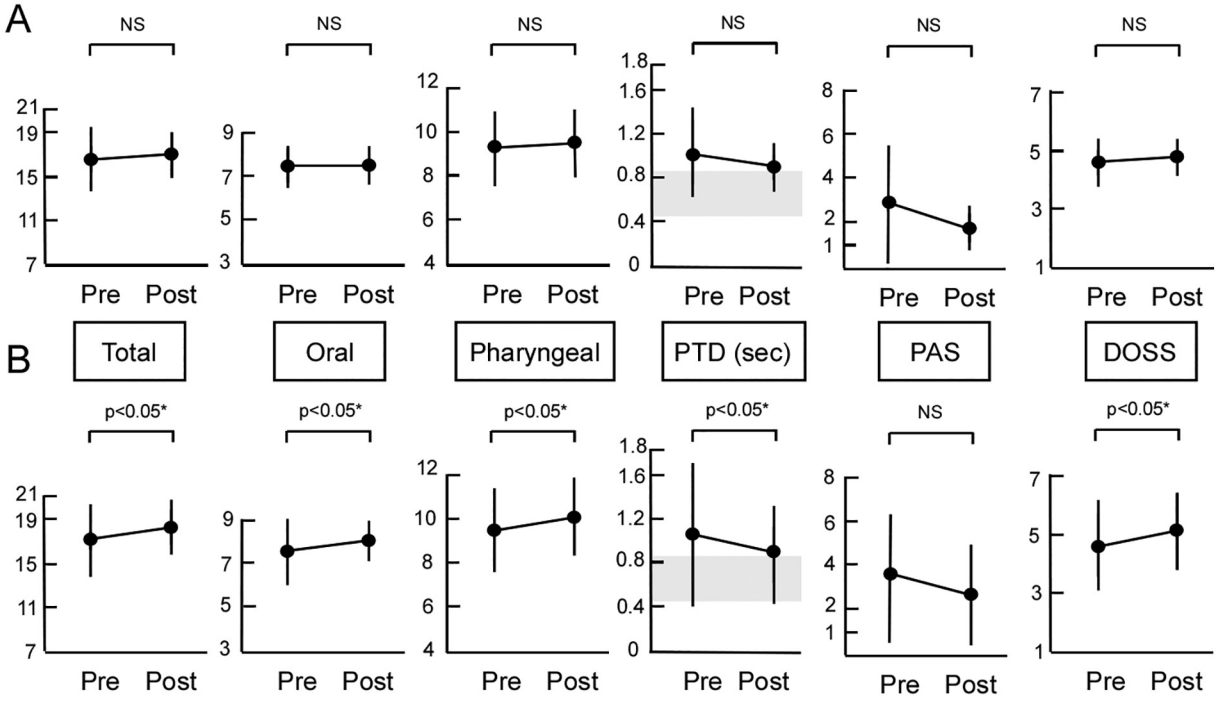

Fig. 3. Swallowing function in 20 already-treated patients with Parkinson's disease before (pre) and after (post) add-on application of an oral levodopa (A, $N = 6$) or a rotigotine transdermal patch (B, $N = 14$). Videofluoroscopic (VF) examinations revealed no significant improvements (Wilcoxon signed-rank test) in any measures in the levodopa group (p < 0.05* or p < 0.01**), but significant improvements in total scores, scores during the oral phase and the pharyngeal phase, pharyngeal transit duration (PTD), and Dysphagia Outcome and Severity Scale (DOSS) scores in the rotigotine group (p < 0.05* or $p < 0.01$**). The Penetration-Aspiration scale (PAS) scores did not significantly improved. The shaded area in PTD indicates the normal range.

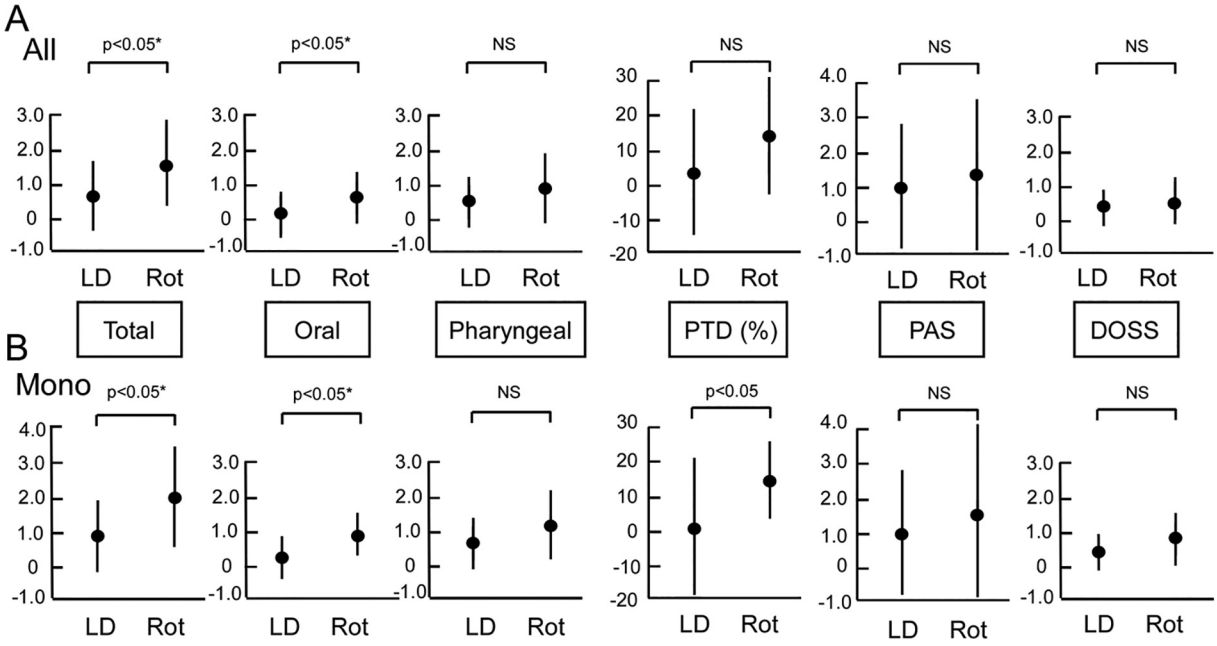

Fig. 4. The comparison of swallowing functions between the group for levodopa treatment (LD) and that for rotigotine (Rot) in 50 patients with Parkinson's disease (A) and in 30 drug-naïve patients (B). (A) Improvements of total scores and scores during the oral phase were significantly higher in the rotigotine group (Mann-Whitney *U* test, $p < 0.05$*). The improved ratio of pharyngeal transit duration (PTD) was tended to be higher in the rotigotine group than in the levodopa group, but did not reach statistical significance ($p = 0.053$). Improvements of scores during pharyngeal phase, Penetration-Aspiration scale (PAS) scores and the Dysphagia Outcome and Severity Scale (DOSS) scores did not differ between the treatment groups. (B) Improvements of total scores and scores during the oral phase were significantly higher in the rotigotine group (Mann-Whitney *U* test, $p < 0.05$*). In addition, the improved ratio of pharyngeal transit duration (PTD) was significantly higher in the rotigotine group than the levodopa group ($p < 0.05$*).

of a previous meta-analysis [5]. Prolonged PTD usually reflects abnormal pharyngeal functions, but it may be partially influenced by oral phase dysfunctions, as in some central nervous system disorders, including stroke [20]. The initiation and driving force of the pharyngeal phase are attributed to a rapid posterior piston-like motion of the tongue, an organ that also plays a major role in the oral phase [21]. The relationship between tongue movements and pharyngeal functions was further supported by a finding that a greater resection of the tongue base in patients with oral cancers was associated with more frequent aspiration [22]. We thus speculate that the inconsistent PTD might be partly associated with the inconsistent improvement in oral phase scores. Another reason may be the fluctuation of the effectiveness of levodopa, owing to reasons such as the no-on or delayed on phenomenon. Despite no considerable inter-daily or intra-daily variations of the observed symptoms, VF examination might not have been performed in the best-on state in our patients. Contrary to the conclusion of a previous meta-analysis [5], our results showed that oral levodopa improved other measures of pharyngeal functions, such as scores during the pharyngeal phase and PAS scores. These results were consistent with reported findings, even in the studies included in the meta-analysis, where pharyngeal residues were reduced [8], and PTD improved in a subset of patients (seven with the most abnormal results among 15 patients) [7]. These findings suggested that oral levodopa also exerts some considerable effects on swallowing, with less consistent effects than rotigotine.

We found that the effects of rotigotine on swallowing may be even clearer in drug-naïve patients who showed that all measures of swallowing functions on VF evaluations were significantly improved by the application of a rotigotine transdermal patch, while not all measures were improved by oral levodopa. Improved ratios of PTD were also seen between the treatment groups. In addition, the responder rates were higher in the rotigotine group than in the levodopa group. The effectiveness of rotigotine on swallowing in 15 drug-naïve patients supported the finding of our previous study that included only 6 patients.

In the patients who received add-on therapy, we found for the first time that most measures of VF evaluations improved by rotigotine, while no significant difference was observed in patients treated with levodopa. Of course, this negative result may be attributed to the small number of patients enrolled. Nonetheless, the positive result in the rotigotine add-on therapy suggests that rotigotine was also effective in

Table 2
The responder rates between patients treated with levodopa and those with rotigotine.

	Total	Oral	Pharyngeal	PTD	PAS	DOSS
Initial + Add-on						
Levodopa (N = 21)	10 (47.6)	4 (19.0)	8 (38.1)	11 (52.4)	8 (38.1)	8 (38.1)
Rotigotine (N = 29)	21 (72.4)	14 (48.3)*	15 (51.7)	27 (93.1)**	10 (34.5)	14 (48.3)
Initial						
Levodopa (N = 15)	8 (53.3)	3 (20.0)	7 (46.7)	7 (46.7)	6 (40.0)	7 (46.7)
Rotigotine (N = 15)	13 (86.7)	9 (60.0)*	10 (66.7)	15 (100)**	6 (40.0)	9 (60.0)
Add-on						
Levodopa (N = 6)	2 (33.3)	1 (16.7)	1 (16.7)	4 (66.7)	2 (33.3)	1 (16.7)
Rotigotine (N = 14)	7 (50.0)	5 (35.7)	5 (35.7)	12(85.7)	4 (28.6)	5 (35.7)

*, **, The responder rate was significantly higher in the rotigotine group than the levodopa group (Fisher's exact test, *, $p < 0.05$; **, $p < 0.01$).

improving swallowing of previously treated patients.

Surprisingly, only a small dose of rotigotine (2 mg/day) improved swallowing function in both drug-naïve and treated patients. One plausible reason may include a demographic difference in body weight between the previous studies and ours. Patients with larger weight generally need larger doses for the same effect. In a reported clinical trial in the US, the mean body weight was 81 kg [23], while the mean body weight in this study in Japan was only 53.0 kg (65% of that in the US). Another demographic factor might include skin permeability, as reported for other medicines [24]. One can speculate the attribution of a “placebo effect” to the observed improved response, as this was an open-label study. However, swallowing function was evaluated by VF examinations with evaluators blinded to all clinical details, which might minimize placebo effects. A small dose of rotigotine may therefore have exerted beneficial effects in our study.

Why only apomorphine (in previous studies) and rotigotine (in the present study) but not other dopamine agonists have been reported to exert beneficial effects on swallowing functions remains unknown; however, the high specificities of apomorphine and rotigotine to dopamine receptor subtypes might be related to such effects. Apomorphine and rotigotine have stronger affinities to the D1 receptor (pKi = 8.8 and 9.2, respectively) than other widely used anti-Parkinson agents, such as ropinirole (pKi < 5.0) and pramipexole (pKi < 5.0) [19]. Feeding problems were found in mice lacking the dopamine D1 receptor, but not in mice lacking the dopamine D2 receptor [25]. Guinea pigs treated with a specific D1 inhibitor had impaired swallowing function [26]. These findings might be related to the improved responses of dysphasia to apomorphine and rotigotine.

In conclusion, we found that rotigotine (levodopa equivalent dose, 60 mg) was more consistently effective than 200 mg/day oral levodopa in improving swallowing functions in drug-naïve patients with PD and those who underwent add-on treatment, thereby suggesting the importance of CDS. To prove the effectiveness of higher-dose rotigotine, further studies are needed. While the parameters of VF examination associated with a history of aspiration pneumonia are important, this study included only two patients with a history of aspiration pneumonia, and thus, the data were inadequate for statistical analysis. Our study has several limitations, such as the small number of patients enrolled, especially in the levodopa-add-on group; its retrospective nature; and the fact that the patients were not randomly assigned to the groups. Nonetheless, our results may warrant future large-scale, prospective studies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.07.003.

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Declaration of Competing Interest

Potential conflicts of interest included:

M. Hirano has received funding for speaker honoraria from Daiichi Sankyo, Eisai, Otsuka Pharmaceutical, Sanofi, Shire; has received Grants-in-Aid from Japan's Ministry of Education, Culture, Sports, Science and Technology; and has received research support from Kindai University and the Japan ALS Association.

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