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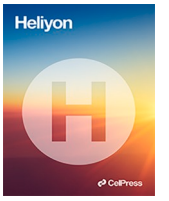

The effect of rasagiline on swallowing function in Parkinson's disease

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ABSTRACT

Dysphagia, a potentially fatal symptom of Parkinson's disease, is characterized by frequent silent aspiration, a risk factor for aspiration pneumonia. The transdermal dopamine agonist rotigotine alleviates dysphagia in patients with Parkinson's disease and is more effective than oral levodopa, suggesting the importance of continuous dopaminergic stimulation during swallowing. Rasagiline is a monoamine oxidase B (MAOB) inhibitor that facilitates continuous dopaminergic stimulation. We hypothesized that MAOB inhibition by rasagiline would be effective in improving swallowing function in patients with early- and mid-to late-stage Parkinson's disease. To this end, we performed an analytical observational study to determine the effects of rasagiline (1 mg/day) on swallowing function using videofluoroscopic swallowing study. This open-label, evaluator-blinded study enrolled 32 patients with Parkinson's disease, among whom 19 were drug-naïve and 13 were receiving add-on therapy. Our results showed that rasagiline significantly improved all swallowing measures during the oral and pharyngeal phases, including oral transit time and pharyngeal transit time, in all enrolled patients. Similar results were found in drug-naïve and mid-to late-stage patients, with no intergroup differences. In conclusion, drugs capable of continuous dopaminergic stimulation may effectively improve swallowing function in patients with Parkinson's disease, with similar effects in early- and mid-to late-stage Parkinson's disease. This study has been the first to show that rasagiline significantly improves swallowing function in mid-to late-stage patients receiving add-on therapy.

1. Introduction

Parkinson's disease (PD), one of the most common neurodegenerative diseases, is characterized by motor symptoms, such as rhythmic shaking of the limbs (tremor), increased muscle tone (rigidity), reduced spontaneous movement (akinesia), and unsteady gait. In addition, patients with PD exhibit non-motor symptoms, including autonomic disturbances. The pathological hallmark of this

Abbreviations: DOSS, the Dysphagia Outcome and Severity Scale; IDDSI, the International Dysphagia Diet Standardisation Initiative; LED, levodopa equivalent dose; MAOA, monoamine oxidase A; MAOB, monoamine oxidase B; OTT, oral transit time; PAS, Penetration-Aspiration scale; PD, Parkinson's disease (PD); PTT, pharyngeal transit time; UPDRS-III, part III of the Unified Parkinson's disease Rating Scale.

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disease is the degeneration of dopaminergic neurons.

Abnormal swallowing, or dysphagia, is a potentially fatal symptom of PD that is characterized by frequent silent aspiration, a risk factor for aspiration pneumonia [1–3]. Swallowing function during the oral and pharyngeal phases are especially important to avoid such a serious complication [4]. The oral phase is characterized mainly by voluntary movements, whereas the pharyngeal phase is associated mainly with the sequential reflexes of the striatal muscles triggered by pharyngeal sensory inputs [4,5]. PD affects voluntary movements as well as pharyngeal sensation, leading to dysphagia [4,5].

The most commonly used medication for PD is levodopa, which crosses the blood–brain barrier and is converted into dopamine in the neurons. This medication may lead to improvements in swallowing efficiency, with some controversial results having been reported [5,6]. Dopamine agonists, which directly stimulate dopamine receptors in neurons, reduce symptoms of PD. In fact, studies show that dopamine agonists apomorphine and rotigotine alleviate dysphagia in patients with PD [4,7–9] and improve involuntary pharyngeal function [4]. A dosage of 2 mg/day of transdermal rotigotine (levodopa equivalent dose [LED], 60 mg/day) is more effective than 200 mg/day of oral levodopa for dysphagia, suggesting the importance of continuous dopaminergic stimulation in improving swallowing function [8]. However, the effects of other medications for PD on dysphagia remain unclear [5]. Despite their effectiveness, dopamine agonists have rare but serious adverse effects, such as sudden onset of sleep that precludes patients from driving [10]. Thus, medications for PD that induce continuous dopaminergic stimulation with few adverse events are advisable. Recently, monoamine oxidase B (MAOB) inhibitors that block the synaptic degradation of dopamine and thus facilitate continuous dopaminergic stimulation have been increasingly used for patients with PD [11,12]. Although our previous small-scale study including nine drug-naïve patients suggested that the MAOB inhibitor rasagiline was effective for mild dysphagia in PD [12], larger-scale investigations including patients with mid-to late-stage PD are needed to achieve a definitive conclusion.

We hypothesized that MAOB inhibition by rasagiline would be effective in improving swallowing function in early- and mid-to late-stage PD. To this end, the effects of rasagiline on swallowing function were examined using videofluoroscopic swallowing study in this open-label, evaluator-blinded study with 32 patients with PD, among whom 19 were drug-naïve and 13 were receiving add-on therapy.

2. Patients and methods

2.1. Patients

We employed an analytical observational study design to determine the effects of rasagiline (1 mg/day) on swallowing function using videofluoroscopic swallowing study. This study enrolled 32 consecutive Japanese patients with PD (19 men and 13 women; mean age ± SD, 74 ± 8 years), among whom 19 were drug-naïve and 13 were receiving add-on therapy. Their characteristics are summarized in Table 1. All patients were diagnosed with PD by board-certified neurologists in accordance with the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria and had a Hoehn–Yahr grade of II to IV. The included patients received 1 mg/day of oral rasagiline and underwent videofluoroscopic swallowing study before and after treatment. In this study, patients who had not received any medication for PD were considered early-stage patients, whereas those with a history of PD for more than 5 years or required ≥300 mg/day of LED to maintain daily activities were considered mid-to late-stage patients. We excluded patients with apparent dementia, signs of upper motor neuron disease, painful or debilitating disorders, and a history of stroke. Cognitive tests were not always performed because patients did not report cognitive decline.

2.2. Treatment protocol

In this open-label, evaluator-blinded study, all 32 patients with PD received 1 mg/day of oral rasagiline (once a day) and continued the same dosage throughout this study. This was a retrospective observational study, but not an intervention study. Among the included patients, 19 were drug-naïve and 13 had received medications other than rasagiline. No PD medications were changed during rasagiline treatment in this study. The patients visited the hospital around 3 months after rasagiline administration given a study suggesting that this medication was maximally effective after at least 3 months [13].

Table 1
Demographics of patients with Parkinson's disease before rasagiline treatment.

Group	Mono-therapy	Add-on	Total
Patient number	19	13	32
Sex	M14, F5	M5, F8	M19, F13
Age of examination (yr)	73 ± 8	75 ± 7	74 ± 8
Age of onset (yr)	71 ± 9	67 ± 11	69 ± 10
Disease duration (yr)	2 ± 2	8 ± 7	4 ± 5
Hoehn-Yahr	2.5 ± 0.5	2.9 ± 0.5	2.7 ± 0.5
UPDRS III	16 ± 4	20 ± 6	18 ± 5
LED (mg/day)	0	542 ± 252	213 ± 305

UPDRS III, Unified Parkinson's Disease Rating Scale part III; LED, levodopa equivalent dose; Values are mean ± SD.

Table 2
The Japanese scale of videofluoroscopic swallowing study.

Oral phase (normal = 9)	
Closure of the lips	3, 2, or 1
Bolus formation	3, 2, or 1
Bolus transport	3, 2, or 1
Pharyngeal phase (normal = 12)	
Constriction of the pharynx	3, 2, or 1
Elevation of the larynx	3, 2, or 1
Bolus stasis at the valleculae or the pyriform sinus	3, 2, or 1
Aspiration	3, 2, or 1
Total score (normal = 21)	

The Japanese scale, a scale established by the Japanese Society of Dysphagia Rehabilitation; 3 = normal; 2 = mildly affected; 1 = severely affected.

2.3. Ethics and informed consent

This study was approved by the Institutional Review Board of Kindai University (IRB#16-011). All participants provided written informed consent to publish their clinical data.

2.4. Videofluoroscopic swallowing study

All patients were evaluated before and 3.3 ± 1.1 months (mean ± SD) after rasagiline treatment. Videofluoroscopic swallowing study was performed during "on" time in accordance with a previous method with slight modification [14,15]. The subjects swallowed a diluted solution of barium (5 mL) three times. Patients who did not have a severe swallowing problem, as indicated by the procedure and rating scales described below, swallowed a concentrated solution of barium three times. During this step, the amount was not restricted, and the subject were requested to swallow as they normally do. Afterward, the patients were requested to swallow 3 g of barium jelly or 5 mL of barium with a commercial xanthan gum-based thickener. The consistency of the diluted and concentrated solutions of barium was Level 0 on the International Dysphagia Diet Standardisation Initiative (IDDSI) [16], whereas that of barium with a commercial xanthan gum-based thickener was IDDSI Level 1. The worst scores were obtained for each scale as described below. Videofluoroscopic results were evaluated according to an excerpt of a Japanese scale established by the Japanese Society of Dysphagia Rehabilitation that had been accepted in many Western journals (Table 2, [8,9,17,18]) and the Dysphagia Outcome and Severity Scale (DOSS) [15]. The Japanese scale assesses lip closure, bolus formation, bolus transport during oral phase, pharynx constriction, larynx elevation, bolus stasis at the vallecular and pyriform sinuses, and aspiration during the pharyngeal phase. The following three-point scale was used to semi-quantify each variable during a videofluoroscopic swallowing study series: 3 (normal), 2 (disturbed), and 1 (severely disturbed). When the Japanese scale was used, the oral phase (3 = severely affected and 9 = normal) and pharyngeal phase (4 = severely affected and 12 = normal) were separately evaluated, and their values were summed to obtain the total score. DOSS (1 = severely affected and 7 = normal) is widely used internationally but cannot separately evaluate the oral and pharyngeal phases [15]. We did not clearly define dysphagia in this study given that we included the patients with PD irrespective of dysphagic state. Patients with DOSS scores of ≤5 literally had mild but obvious dysphagia, but this study also included patients with DOSS scores of 6 or 7 who had abnormalities in the Japanese scale, oral transit time (OTT) or pharyngeal transit time (PTT). The Penetration-Aspiration scale (PAS) is an 8-point scale (1 = no penetration and 8 = aspiration with no ejection efforts) [19]. Each patient was scored independently by one speech language pathologist and one neurologist who were blinded to all clinical details. Both evaluators had more than 10 years of experience in swallowing evaluation. Should score discrepancies emerge, an additional neurologist who was also a swallowing expert determined which score was appropriate. Assessment of the intra- and inter-rater reliability of the three evaluators analyzing the videofluoroscopic swallowing study scores showed significant correlations within and between the evaluators [20].

OTT was calculated from the time backward tongue movement began to the time the bolus head arrived at the ramus of the mandible [4]. PTT was calculated from the time the bolus head arrived at the ramus of the mandible until the time the tail of the bolus passed through the upper esophageal sphincter [4]. OTT and PTT were measured during the second instance at which all patients swallowed 5 mL of diluted barium. Institutional normal values for OTT and PTT were obtained from our previous study using 6 healthy controls (age 65 ± 14 years) as the standard [12].

2.5. Evaluation of parkinsonism

Parkinsonism was evaluated using the Hoehn–Yahr scale and part III (motor examination) of the Unified PD Rating Scale (UPDRS-III). All patients were evaluated before and 3.3 ± 1.1 months (mean ± SD) after rasagiline treatment. Mid-to late-stage patients were evaluated during "on" time. Drug-naïve patients exhibited slight motor fluctuations after the treatment.

2.6. Statistical analyses

The abovementioned scores and times before treatment were compared to those after treatment. Ordinal data, such as total scores, scores during oral and pharyngeal phases, DOSS scores, UPDRS-part III scores, and Hoen–Yahr scores were subjected to the Wilcoxon signed-rank test [9,12] because nonparametric statistics were applied. OTT and PTT served continuous values, which were not distributed normally in our previous studies [9,12], and were thus also subjected to the Wilcoxon signed-rank test. We considered a p value of <0.05 statistically significant. Statistical analyses were performed using SPSS software version 22.

3. Results

3.1. Improvement in swallowing function among the 32 patients with PD

The oral phase, pharyngeal phase, and total scores of the Japanese scale and DOSS scores improved significantly in all 32 patients with PD ($p < 0.01$, Wilcoxon signed-rank test; Fig. 1). After rasagiline treatment, OTT improved significantly, whereas PTT improved mildly but significantly ($p < 0.01$, Wilcoxon signed-rank test; Fig. 1). Rasagiline treatment significantly improved the PAS scores in all patients (Wilcoxon signed-rank test; Fig. 1).

3.2. Improvements in the swallowing function of drug-naïve patients and mid-to late-stage patients receiving add-on therapy

The oral phase, pharyngeal phase, and total scores of the Japanese scale improved significantly in the 19 drug-naïve patients with PD and 13 mid-to late-stage patients receiving add-on therapy ($p < 0.05$, Wilcoxon signed-rank test; Fig. 2). After rasagiline treatment, DOSS scores and OTT also significantly improved, whereas PTT showed a mild but significant improvement in drug-naïve patients and mid-to late-stage patients receiving add-on therapy ($p < 0.05$, Wilcoxon signed-rank test). No significant improvement of the PAS score was detected in drug-naïve patients ($p = 0.115$, Wilcoxon signed-rank test) or in patients with mid-to late-stage disease ($p = 0.161$, Wilcoxon signed-rank test; Fig. 2), possibly because of the insufficient number of participants for statistical testing. A comparison between drug-naïve patients and mid-to late-stage patients receiving add-on therapy showed no significant difference in the extent of improvement in the corresponding measures (Mann–Whitney U test; Fig. 3).

3.3. Improvements in motor function as evaluated by the Hoehn–Yahr scale and UPDRS-III scores

After rasagiline treatment, motor function improved in all 32 patients as indicated by their UPDRS-III scores (16 ± 4 vs. 11 ± 4); however, no significant change was observed in their Hoehn–Yahr scale scores. Changes in the UPDRS-III scores were not significantly associated with the videofluoroscopic swallowing study scores, DOSS scores, OTT, or PTT.

4. Discussion

This open-label, evaluator-blinded study in 32 patients with PD showed that rasagiline significantly improved swallowing function by improving all measures on the current videofluoroscopic swallowing study evaluation. Medications for PD improve swallowing during the oral phase, which is characterized mainly by voluntary movements [5]. Indeed, oral phase scores were improved after rasagiline treatment, which was also supported by the improved OTT. The reduced UPDRS-III scores implied an improvement in voluntary movements affected by parkinsonism. However, the extent to which swallowing function improved was not correlated with changes in the UPDRS-III scores, suggesting that other factors, including impairment in pharyngeal sensation, may be involved [21]. Rasagiline improved PTT, which is mainly associated with the sequential reflexes of the striatal muscles during the pharyngeal phase. A significant increase in the pharyngeal phase score was observed in the present study but not in our previous work [12], suggesting an

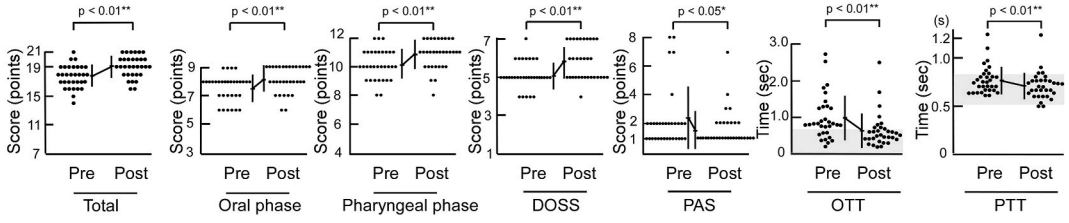

Fig. 1. Results of videofluoroscopic swallowing study in 32 patients with Parkinson's disease before (pre) and 3.3 ± 1.1 months after (post) treatment with rasagiline. Videofluoroscopic swallowing study showed significant improvements (*$p < 0.05$ or **$p < 0.01$, Wilcoxon signed-rank test) in the total, oral phase, pharyngeal phase scores, the Dysphagia Outcome and Severity Scale (DOSS) scores as well as the Penetration-Aspiration scale (PAS) scores. Significant improvements in oral transit time (OTT) and pharyngeal transit time (PTT) were observed after treatment (**$p <$ 0.01, Wilcoxon signed-rank test). Shaded regions indicate normal ranges for OTT and PTT. Bar indicates mean ± SD. The total score ranges from a minimum of 7 to a maximum of 21 points; the oral phase score ranges from 3 to 9, the pharyngeal score from 4 to 12, the PAS from 1 to 8, and the DOSS from 1 to 7.

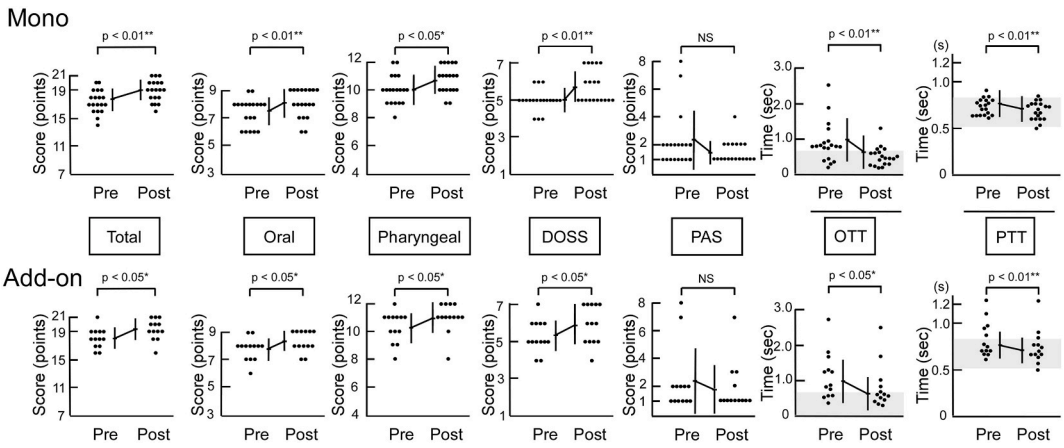

Fig. 2. Results of videofluoroscopic swallowing study in 19 drug-naïve patients (upper panel) and 13 mid-to late-stage patients receiving add-on therapy (lower panel) before (pre) and after (post) treatment with rasagiline. Videofluoroscopic swallowing study showed significant improvements (*$p < 0.05$ or **$p < 0.01$, Wilcoxon signed-rank test) in the total, oral phase, and pharyngeal phase scores, as well as the Dysphagia Outcome and Severity Scale (DOSS) scores. No significant improvement (NS) of the Penetration-Aspiration scale (PAS) scores was detected in drug-naïve patients or in patients with mid-to late-stage disease (Wilcoxon signed-rank test). Significant improvements in oral transit time (OTT) and pharyngeal transit time (PTT) were observed after treatment in both groups (*$p < 0.05$ or **$p < 0.01$, Wilcoxon signed-rank test). Shaded regions indicate normal ranges for OTT and PTT. Bar indicates mean ± SD. The total score ranges from a minimum of 7 to a maximum of 21 points; the oral phase score ranges from 3 to 9, the pharyngeal score from 4 to 12, the PAS from 1 to 8, and the DOSS from 1 to 7.

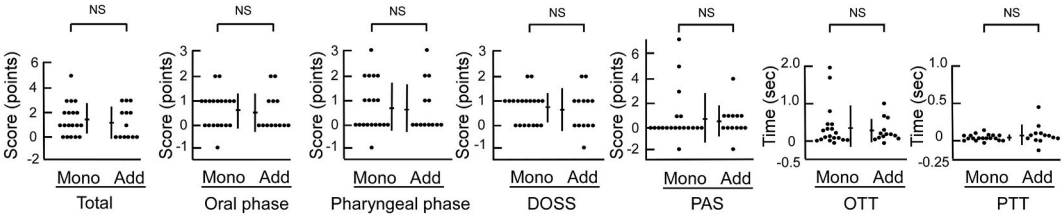

Fig. 3. Comparison of the extent of swallowing function improvement after rasagiline treatment between the 19 drug-naïve patients (upper panel) and the 13 patients receiving add-on therapy (lower panel). Videofluoroscopic swallowing study showed no significant difference (NS) in the total, oral phase, and pharyngeal phase scores, the Dysphagia Outcome and Severity Scale (DOSS) scores, the Penetration-Aspiration scale (PAS) scores, oral transit time (OTT), and pharyngeal transit time (PTT) (Mann–Whitney *U* test). Bar indicates mean ± SD.

increase in statistical power with this large-scale investigation. Notably, we found improvements in the PAS score, a predictor of aspiration pneumonia [22], after rasagiline treatment. We thus speculate that increased dopaminergic stimulation facilitates the pharyngeal and oral phases, thereby improving swallowing function.

The effect of rasagiline was separately evaluated in early- and mid-to late-stage patients. Almost all measures improved in both groups with no intergroup difference. This finding suggests that the effects of rasagiline was similar in early-stage and mid-to late-stage PD. However, the mid-to late-stage patients were still relatively mildly affected and only had 8 years of PD history and 20 points on their UPDRS-III scores. Hence, the effects of rasagiline for dysphagia in further advanced-stage patients remains to be investigated.

This study provides additional evidence that continuous dopaminergic stimulation may be beneficial for swallowing function in PD. Although continuous dopaminergic stimulation is achieved by rasagiline in patients treated with levodopa [11], this condition has not been observed in rasagiline monotherapy. Rasagiline inhibits MAOB and increases neuronal dopamine levels in a more physiological manner than oral levodopa, which usually causes pulsatile dopaminergic stimulation [23]. Rotigotine transdermal patch, an ideal drug for continuous dopaminergic stimulation, improves swallowing when administered as monotherapy and add-on therapy [8,9]. Thus, we speculate that rasagiline, as either monotherapy or add-on therapy, can facilitate continuous dopaminergic stimulation to improve the existing swallowing function and delay the future development of dysphagia.

Other mechanisms underlying the beneficial effect of rasagiline on swallowing function may include monoamine oxidase A (MAOA) inhibition, which is associated with serotonin catabolism. Rasagiline increases serotonin levels in the rodent brain [24,25] and causes MAOA inhibition in humans [26]. Based on these findings, rasagiline may increase serotonin levels in the human brain. The association between serotonin and swallowing function is supported by an *in vivo* study, which found that mice lacking brain-derived serotonin exhibited swallowing dysfunction [27]. In humans, increased serotonin levels have been associated with improved swallowing in several diseases, such as ischemic stroke [28]. We thus speculate that MAOA inhibition by rasagiline may be related to its beneficial effects on swallowing function.

The limitations of this study include the still relatively small number of patients enrolled. In addition, patients with relatively mild parkinsonism who could visit our hospital were enrolled. Given the retrospective nature of this study, the findings should be interpreted with caution.

In conclusion, a drug for continuous dopaminergic stimulation, rasagiline, may be effective in improving swallowing function in PD. To our knowledge, this has been the first study to show that rasagiline significantly improves swallowing function evaluated using videofluoroscopic swallowing study in mid-to late-stage PD. Future studies are needed to clarify the effects of rasagiline on dysphagia in patients with further advanced-stage PD.

Data availability statement

All data analyzed in this study will be made available from the corresponding author upon request. The data was not deposited into a publicly available repository.

CRediT authorship contribution statement

Makito Hirano: Investigation, Project administration, Writing – original draft, Writing – review & editing, Data curation. **Makoto Samukawa:** Data curation. **Chiharu Isono:** Data curation. **Susumu Kusunoki:** Supervision, Writing – review & editing. **Yoshitaka Nagai:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Makito Hirano reports a relationship with Sumitomo, Ono, Otsuka, Novartis, Kyowa-Kirin, Eisai, and Takeda that includes: funding grants and speaking and lecture fees. Makoto Samukawa reports a relationship with Takeda, FP, Eisai, and Sumitomo Pharmaceutical that includes: speaking and lecture fees. Susumu Kusunoki reports a relationship with Japan Blood Product Organization and CSL Behring that includes: speaking and lecture fees. Yoshitaka Nagai reports a relationship with Sumitomo, Kyowa-Kirin, Tanabe-Mitsubishi, Amgen, Takeda, Otsuka, Fujimoto, Daiichi-Sankyo, Esai, and Chugai that includes: funding grants and speaking and lecture fees.

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