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ORIGINAL ARTICLE

A Pilot Study of Respiration and Swallowing Integration in Parkinson's Disease: "On" and "Off" Levodopa

Anthony Lim · LiPyn Leow · Maggie-Lee Huckabee · Chris Frampton · Tim Anderson

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Abstract Parkinson's disease is associated with both swallowing and respiratory dysfunction, increasing the risk of aspiration and pneumonia. Previous studies have shown improvements in measurements of swallowing and respiration with levodopa; however, the studies are small and some studies show conflicting reports. The aim of this study was to further investigate the effect of levodopa on respiration. Ten patients with Parkinson's disease were tested "On" and "Off" levodopa. Assessments included Unified Parkinson's Disease Rating Scale (UPDRS), coordination of swallowing and respiration, timed-test of swallowing, lung function testing, and, qualitative assessment of swallowing. There was a nonsignificant trend to lower volume per swallow when "On" levodopa, significant reduction in lung function when "On" levodopa, but no difference in coordination of swallowing and respiration or qualitative assessment of swallowing. There was a significant increase in motor examination score of the UPDRS when "Off" levodopa compared to "On." There may be a reduction in efficiency of swallowing with levodopa medication without any apparent increase in risk of aspiration. These pilot data suggest that further evaluation with larger numbers of participants is justified.

Keywords Parkinson's disease · Levodopa · Deglutition · Respiration · Deglutition disorders

James Parkinson's first description of Parkinson's disease (PD) in 1817 included difficulty eating food, impaired muscles of swallowing, sialorrhea, and a patient "who fetched his breath rather hard" [1]. The disease affects 1/1000 of the population, and life expectancy with current treatment is only 1.5 years less than the general population [2]. However, in PD there is a higher risk of pneumonia as a cause of death, six times the normal population [2]. This is thought to be due to a combination of chronic immobilization and swallowing impairment [3].

Previous studies have shown that 31%–100% of patients with PD have some problem with swallowing [4–8]. Abnormalities detected by clinical and radiographic swallowing examination include prolonged transit times, delayed swallowing reflex, impaired palatal elevation, difficult and decreased tongue movements, poor bolus formation, incomplete upper esophageal sphincter relaxation, impaired epiglottis motility, regurgitation, vallecula and pyriform sinus pooling, impaired laryngeal adduction, tracheal penetration, and aspiration [4–13]. Pharyngeal manometry has revealed a higher hypopharyngeal intrabolus pressure and lower pharyngeal contraction pressures [11]. Vocal fold bowing is a common finding in patients with PD, and in many to the degree that vocal fold

Work was performed at the Van der Veer Institute for Parkinson's and Brain Research, Christchurch, New Zealand.

A. Lim · C. Frampton · T. Anderson
Department of Medicine, Christchurch School of Medicine, Christchurch, New Zealand

L. Leow · M.-L. Huckabee
Department of Communication Disorders, University of Canterbury, c/o Van der Veer Institute, 16 St. Asaph Street, Christchurch, New Zealand

A. Lim · L. Leow · M.-L. Huckabee (✉)
Van der Veer Institute for Parkinson's and Brain Research, Christchurch, New Zealand
e-mail: maggie-lee.huckabee@canterbury.ac.nz

T. Anderson
Department of Neurology, Christchurch Hospital, Christchurch, New Zealand

entrainment is decreased [14]. Drooling and difficulty swallowing saliva are present in up to 78%, even though patients with PD secrete the same or less than controls [5]. Symptoms of dysphagia are worse for solids than for liquids [5] and increase with stress [12], but most abnormalities detected by investigation are asymptomatic [12]. Swallowing efficiency is higher in patients who have dyskinesis; however, this may be explained by the higher doses of levodopa medication [15]. Edwards et al. [7] suggested that dysphagia may be due to involvement of the dorsal motor nucleus of the vagus nerve and of Lewy bodies in the myenteric plexus of the esophagus. Symptoms can be accounted for by rigidity and bradykinesia of oropharyngeal muscles [4, 8]. The literature lacks agreement on the association between severity of PD and presence and severity of dysphagia. Some studies have found no association [11, 12], whereas others have found worsening dysphagia with increasing severity of PD [4, 10]. It is thought that patients may experience symptoms of dysphagia later in disease course of PD compared to other parkinsonian disorders [16]. Even so, because of the poor correlation between reported symptoms and instrumental assessments of dysphagia, presymptomatic dysphagia may be present and unidentified.

Of those with swallowing problems, 30% have signs of aspiration [5]. Silent tracheal aspiration has been found in 15%–46% of patients with PD [6, 17]. Pinnington et al. [9] found that only 80% of patients with PD have an expiration following swallows compared with 99% in the normal population. In a study of stroke patients [18], those who had aspiration as seen on videofluoroscopy have a higher chance of developing pneumonia. Although aspiration and dysphagia increase the risk of pneumonia, oral hygiene is also a major risk factor, especially in combination with aspiration [19]. The study by Langmore et al. [19] showed the risk factors for aspiration pneumonia also included dependency for feeding and oral care, number of decayed teeth, tube feeding, comorbidities, multiple medications, and smoking.

Respiratory dysfunction is still a significant cause of morbidity and mortality in PD [20, 21]. Abnormalities are usually due to upper airway obstruction, restrictive defects, or problems with ventilatory control [20, 21]. Lung function testing in patients with PD has shown a decreased FVC, reduced FEV_1, higher RV, and reduced peak inspiratory and expiratory flows [22–24]. Upper airway obstruction is present in 24%–37% of patients with PD, most of whom are asymptomatic [23–25]. Other studies have shown mostly restrictive patterns [22], these being ascribed to rigidity of respiratory muscles [20]. Abnormalities in respiration are associated with increasing severity of PD [20, 21].

Dopaminergic medications have been shown to improve almost all measures of lung function [22, 25]. However, there is scant evidence regarding the effects of levodopa on swallowing. The studies that have been performed are small and show only small improvements in dysphagia in a proportion of participants, with decline in function in some [17, 26, 27]. Improvement in other parkinsonian signs from medication has not been a good indicator of improvement in dysphagia [17]. Hunter et al. [27] suggested that swallowing abnormalities are not solely related to dopamine deficiency.

This pilot study aimed to investigate respiration and swallowing in PD to help clarify the effect of levodopa on these measures.

Methods

Participants

Ten patients were recruited from Parkinson's disease outpatient clinics located at a freestanding Parkinson's disease research facility. Inclusion criteria were patients with Parkinson's disease currently treated with levodopa. Exclusion criteria included those who had smoked within the last five years, had other neurologic impairments (including past stroke, multiple sclerosis, and other neurodegenerative diseases), dementia (as assessed by a score of less than 26/30 on the Mini Mental Status Examination), terminal illness, asthma, COPD, other breathing disorders, unstable cardiac conditions, or previous head or neck surgery. The study was approved by the Upper South Regional Ethics Committee (URB/06/02/006), and informed written informed consent was obtained from all participants.

Assessments

Assessments were performed at the Parkinson's disease research facility on each patient in two morning sessions spaced at least one week apart. In one of the sessions participants were in the "On" state, having taken their levodopa medication as usual. In the other session participants were required to be in the "Off" state, achieved by withholding any levodopa medication at least 12 h before assessments were performed. All other medications were continued as normal. Each session was between one to two hours in duration to further ensure that there was no observable wearing off effect during the "On" session. Participants were randomly allocated into two groups by a random number generator, where an odd number placed the participant in group 1, and an even number placed the participant in group 2. This was repeated until an equal number of five participants were allocated into each group. Those in group 1 had their first session "On" levodopa and their second session "Off." Those in group 2 had their first

session "Off" and second session "On" to reduce introduction of potential bias. A dysphagia quality-of-life questionnaire (SWAL-QOL) [28] was given to each participant to complete before the start of the study and returned at their first session.

At each session, assessments were performed in the following order:

Unified Parkinson's Disease Rating Scale (UPDRS) sections II (activities of daily living) and III (motor examination).

Coordination of swallowing and respiration. EMG surface electrodes were placed midline under the chin and a nasal cannula attached to the participant and connected to the Digital Swallowing Workstation v3.0.1 (KayPENTAX, Lincoln Park, NJ). Inspirations and expirations immediately before and after ten swallows of 8 ml of plain tap water from small cups were recorded. "Normal swallows" were defined as swallows that were immediately followed by expiration. The percent of normal swallows, average sEMG amplitude per swallow, and variance between sEMG amplitudes were calculated.

Timed-test of swallowing as described by Hughes and Wiles [29]. While still connected to the workstation, participants were asked to drink 150 ml of plain tap water "as quickly as is comfortably possible." The number of swallows and time from when the water first touched the bottom lip to when the sEMG readings returned to the rest state were recorded. The average volume per swallow, average time per swallow, and swallowing capacity (ml/s) were calculated.

Lung function using standard closed-loop spirometry was performed according to standards set out by the American Thoracic Society [30]. Full instructions were given and a nose clip placed on the participant. With the mouthpiece in, they were instructed to forcefully inspire to full inhalation then immediately forcefully exhale for at least 6 s before a full inhalation again to close the loop. This was repeated so that at least three comparable results were obtained. The best measurements were used for analysis.

Assessment of swallowing was performed using a nasendoscope (Welch Allyn RL-150). Participants ingested in the following order: three trials of 8 ml of dyed water, three trials of 8 ml of dyed nectar-thick fluid (kiwifruit juice), three trials of 8 ml of chocolate pudding, a shortbread biscuit, and 90 ml of dyed water through a straw. Any laryngeal aspiration, laryngeal penetration, residue, or spillage was noted.

Statistical Analysis

Statistical analysis was performed using SPSS v11.5 (SPSS Inc., Chicago, IL) using paired *t* tests and McNemar tests to determine if there was a significant difference between any of the key variables in the "On" and "Off" states.

Results

Subject Characteristics

The ten participants (6 male, 4 female) ranged in age from 51 to 69 years. They were classified within Hoehn and Yahr stages 1–4, with an average duration of Parkinson's disease of 8.5 years (Table 1). Nine of the ten participants performed all assessments to completion. One participant did not perform the qualitative assessment of swallowing because of discomfort from the endoscopy.

Table 1 Participant characteristics

ID	Sex	Age	Years with PD	Levodopa dose (mg/day)	Years on levodopa	SWAL-QOL Score[a]	Hoehn and Yahr	Medications for Parkinson's disease
1	F	51	3	700	0.4	76.1	1	Levodopa/carbidopa, ropinirole, orphenadrine
2	M	67	10	300	1.5	70.3	3	Levodopa/carbidopa, pergolide, selegiline, amantadine
3	F	66	2	400	0.5	78.1	3	Levodopa/carbidopa, pergolide
4	M	66	2	400	0.2	94.3	1	Levodopa/carbidopa, pergolide, amantadine
5	M	69	8	300	6.0	71.6	3	Levodopa/benserazide, pergolide
6	F	67	16	600	6.0	88.5	3	Levodopa/carbidopa, orphenadrine
7	M	59	11	600	2.0	87.4	1	Levodopa/carbidopa, pergolide, benztropine, selegiline, amantadine
8	M	69	13	650	10.0	66.8	4	Levodopa/carbidopa, levodopa/benserazide
9	M	57	9	550	0.8	96.6	2	Levodopa/carbidopa, ropinirole, orphenadrine
10	F	64	11	300	1.0	93.9	2.5	Levodopa/carbidopa, pergolide, orphenadrine
Mean		63.5	8.5	480	2.8	82.4	2.4	

[a] The SWAL-QOL score represents the percent of best possible score

Table 2 Difference between key measures: "Off" levodopa minus "On" levodopa

Measure	Mean value "Off" (SD)	Mean value "On" (SD)	Mean difference "Off"–"On" (95% CI)	*p* value[a]
Unified Parkinson's Disease Rating Scale (UPDRS)				
Section II (Activities of daily living)	12.90 (6.79)	12.30 (6.58)	0.60 (–1.46, 2.66)	0.526
Section III (Motor examination)	25.30 (13.05)	21 (10.68)	4.30 (0.02, 8.58)	**0.049**
Coordination of swallow and respiration				
Percent of normal swallows	91.00 (25.14)	100.00 (0.00)	–9.00 (–26.99, 8.99)	0.287
Average strength of swallow (μV)	64.40 (44.91)	66.04 (47.06)	–1.64 (–17.61, 14.34)	0.822
Variance in strength of swallows	120.14 (167.59)	196.53 (294.84)	–76.39 (–294.77, 142.00)	0.449
Timed test of swallowing				
Number of swallows	9.50 (3.78)	9.90 (2.69)	–0.40 (–1.37, 0.57)	0.373
Time taken (s)	14.70 (8.68)	16.01 (9.46)	–1.31 (–4.76, 2.15)	0.414
Average volume per swallow (ml)	17.67 (5.55)	15.95 (3.35)	1.72 (–0.39, 3.82)	0.098
Average time per swallow (s)	1.50 (0.433)	1.55 (0.60)	–0.05 (–0.36, 0.25)	0.690
Swallowing capacity (mL/s)	13.03 (5.88)	11.75 (4.84)	1.28 (–0.65, 3.21)	0.168
Lung function testing				
FVC (L)	4.19 (0.86)	4.03 (0.83)	0.15 (0.07, 0.23)	**0.002**
FEV_1 (L)	3.29 (0.76)	3.19 (0.75)	0.10 (0.01, 0.20)	**0.035**
FEV_1/FVC	78.2 (3.39)	78.9 (4.46)	–0.70 (–2.61, 1.21)	0.428
FEV_6 (L)	4.08 (0.84)	3.92 (0.83)	0.16 (0.05, 0.26)	**0.009**
PEF (L/s)	7.58 (1.79)	7.21 (1.73)	0.37 (–0.24, 0.98)	0.202
PIF (L/s)	5.13 (2.36)	4.93 (1.62)	0.20 (–1.93, 2.32)	0.840

[a] *p* values taken from the paired *t* test

[b] Compared to the side most affected by Parkinson's disease as determined by the UPDRS

Findings

Tables 2 and 3 summarize the results of the study. In the Unified Parkinson's Disease Rating Scale there was a significant increase in motor examination score (4.3, $p = 0.049$), indicating that, as expected, the participants showed more severe motor signs of Parkinson's disease "Off" levodopa. There was a nonsignificant trend to lower volume per swallow when "On" the medication (1.72 ml, $p = 0.098$), but no differences in other measures of the timed-test of swallowing. Lung function testing showed significant improvements when "Off" medication in FVC (0.15 L, $p = 0.002$), FEV_1 (0.10 L, $p = 0.035$), and FEV_6 (0.16 L, $p = 0.009$), but no significant changes in FEV_1/FVC, peak inspiratory flow, or expiratory flow. No statistically significant differences were observed in coordination of swallowing and respiration. No significant changes or apparent trends were observed in the qualitative assessment of swallowing.

Discussion

Prior research has suggested improvement in swallowing function with levodopa [17, 26, 27]; however, there is scant research regarding the specific association between levodopa and aspiration in Parkinson's disease. The studies that have been performed have not detected any difference in rates of aspiration between "On" and "Off" states [17, 26, 27]. The focus of this research was to further evaluate the risk of aspiration, in particular, the integration of swallowing and respiration "On" and "Off" levodopa.

Motor function was significantly worse when "Off" levodopa than "On" as evidenced by UPDRS scores. This decline, however, was not apparent in rates of laryngeal penetration or tracheal aspiration in the qualitative assessment of swallowing, suggesting that the risk of laryngeal aspiration remains unchanged. However, only a small number of participants were studied, and further investigation with greater numbers of participants and long-term follow-up need to be performed to assess the difference in penetration and aspiration "On" and "Off" levodopa to investigate whether or not there truly is no difference.

There was a nonsignificant trend to lower volume per swallow when "On" levodopa. No differences were observed between other measures in the timed-test of swallowing, including time per swallow and swallowing capacity. Coordination of swallowing and respiration remained unchanged. This suggests that levodopa may reduce the volume the patient can swallow per bolus, without affecting the time taken between swallows, hence only

Table 3 Results from the qualitative assessment of swallowing

ID	Aspiration		Penetration		Residue		Spillage		Vocal fold bowing?
	"Off"	"On"	"Off"	"On"	"Off"	"On"	"Off"	"On"	
1	-	-	-	-	Pudding	Solid	Pudding	-	Yes
2	-	-	-	Solid	Nectar and solid	Nectar and solid	Water	-	No
3	-	Water	-	-	-	-	-	-	No
4	Water, Nectar, ?Solid	-	Water, Nectar, Pudding	?Water	Solid	Solid	-	-	No
5	-	-	-	-	Solid	-	-	-	No
6	-	-	-	-	Solid	Pudding and solid	Water	Water and nectar	No
7	Could not be performed due to discomfort								No
8	-	-	-	-	Pudding and solid	Pudding and solid	-	-	No
9	-	-	-	-	Solid	Solid	-	-	No
10	-	-	Solid	-	Water and solid	Solid	-	Nectar	Yes

Table shows findings for the texture of food ingested (if any present). No statistically significant differences were found on McNemar tests

reducing the swallowing efficiency to some extent. This is inconsistent with prior research that suggests that swallowing efficiency may improve with levodopa [27]. Hunter et al. [27] detected fewer swallows to clear solid boluses after levodopa, although they did find an increase in oral phase and total swallowing times with the medication.

Key measures of lung function significantly declined when "On" levodopa. Nine of the ten participants had reduced function with levodopa medication. However, all the changes in measures were small and did not meet clinical significance based on the American Thoracic Society and European Respiratory Society standardization of lung function testing [31]. All previous studies have shown improvements with levodopa [22–24]. While none have found a decline in lung function with levodopa, some studies describe respiratory dysfunction as a levodopa side effect, possibly due to restrictive or dyskinetic respiratory muscles [20, 21]. In our patient cohort we noted only one participant (participant 6) had dyskinesis when "On" levodopa, but she did not have any while "Off." Our findings may be explained by side effects of levodopa, chance, or unidentified flaws in our method.

In summary, this pilot study found that swallowing efficiency may be reduced with levodopa medication. No association was found between levodopa and coordination of swallowing and respiration, laryngeal penetration, or tracheal aspiration, indicating that the risk of aspiration may remain unchanged. Further studies comprising larger numbers of patients are needed to determine whether the trend in swallowing efficiency is a true effect and to confirm if there really is no difference in risk of aspiration between "On" and "Off" states of levodopa. If it were shown to be the case, the speculation would be that levodopa therapy might actually reduce swallowing efficiency while keeping the risk of aspiration unchanged in patients with PD.

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Anthony Lim MBChB
LiPyn Leow BSc(Hons)
Maggie-Lee Huckabee PhD
Chris Frampton PhD
Tim Anderson BSc(Hons), MBChB, MD, FRACP