EFFECTS OF CENTRAL DOPAMINERGIC STIMULATION BY APOMORPHINE ON VOCAL PARAMETERS IN PARKINSON'S DISEASE

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ABSTRACT

In Parkinsonian patients, abnormal vocal qualities are frequently observed. Previous research has suggested that laryngeal muscle rigidity may be responsible for the vocal symptoms. While rigidity is one of the most responsive symptoms to dopaminergic therapy, studies investigating speech changes following dopaminergic therapy are very limited. In this study, phonatory responses to dopaminergic stimulation were examined using a double-blind, placebo-controlled design. Ten Parkinsonian patients with speech impairment served as subjects. They were given placebo or apomorphine during two consecutive visits. Data were collected at baseline and 30 minutes post-injection during each visit. Subjects produced maximally sustained, and comfortably phonated vowels. Instrumental analysis was used to assess changes in phonatory function. Nonspeech motor functions were assessed using the Unified Parkinson's Disease Rating Scale. While nonspeech motor functions improved significantly following the dopaminergic stimulation, the vocal parameters showed no changes. This suggests that dopaminergic depletion may not be responsible for the laryngeal dysfunction.

1. INTRODUCTION

Idiopathic Parkinson's disease (IPD) is a progressive degenerative disease associated with nigro-striatal dopaminergic deficiency [1]. In this clinical population, speech impairment known as hypokinetic dysarthria is a common complaint [2]. Logemann, Fisher, Bashes, & Blonsky [3] reported that in their study of 200 subjects with Parkinson’s disease, 89% had laryngeal involvement (e.g., soft, breathy and hoarse voice), and 45% had additional articulatory involvement (e.g., slurred speech). Hanson, Gerratt, & Ward [4] observed abnormal laryngeal vibration patterns such as glottic gap and bowing of the vocal folds on phonation in Parkinson’s subjects who demonstrated abnormal voice qualities. Laryngeal tremor has also been found to be frequently associated with IPD [5]. The findings on the observed abnormal phonatory posture have been suggested to be related to increased laryngeal muscle rigidity in these patients [4].

Although the etiology of PD is still unclear, pharmacological treatment has been the choice for managing the symptoms associated with PD [6, 7]. Studies investigating the effect of PD treatment on speech were limited and the findings were inconclusive [8, 9, 10, 11, 12]. Results reported include improved speech intelligibility [10], improved voice quality [11], improved oral muscular movement [8, 10], or no consistent improvement [9, 12]. The disagreement among these studies may be partially attributed to the uncontrolled confounding factors and differences in methodology. These factors and differences are (i) lack of placebo-controls; (ii) difference in previous treatment of L-dopa, e.g., one study reported that none of its subjects were treated with L-dopa before the study while others indicated that all of their subjects had been on L-dopa treatment for some time; (iii) patient's responsiveness to the medication, e.g., one study indicated that three of their nine subjects did not respond to the L-dopa treatment at all while others whose subjects had been on L-dopa treatment did not mention whether those subjects experienced any drug-induced dyskinesias; (iv) speech impairment, e.g., one study indicated that of their nine subjects, only one had a moderate speech impairment while the remaining eight had slight or none; (v) differences in method, e.g., two of the studies measured labial tracing of EMG signals, another measured jaw movement using an optoelectronic technique while the fourth study used a perception scale with no acoustic or kinematic analysis; (vi) differences in stimuli, e.g., single vowel production to paragraph reading. Based on these observations, it seems that a more rigid experimental design should be used to examine the effect of dopaminergic stimulation on speech production.

Rigidity is one of the most responsive symptoms of all experienced by patients with IPD following levodopa treatment [6, 7]. Rigidity has also been suggested to be the source of the observed abnormal phonatory posture in PD [4]. Therefore, it is reasonable to expect improvement in laryngeal function in PD patients if their laryngeal dysfunction is associated with rigidity resulting from nigro-striatal dopaminergic deficiency [1, 4, 7]. In this paper, we report our findings on instrumental analysis of the laryngeal responses to the dopaminergic stimulation by apomorphine in ten IPD patients. The analysis was performed on data obtained in a double-blind, placebo-controlled study investigating the changes in speech function following apomorphine administration. Findings on changes in non-speech motor functions (e.g., limb movement), vocal intensity and duration of sustained vowels, and speech intelligibility scores from the sentence test of the Assessment of Intelligibility of Dysarthric Speech (AIDS) [13] have been previously reported [14, 15].

2. METHODS

Detailed methodology of the study has been reported [14, 15]. However, some relevant brief details are provided below.

2.1. Subjects

Ten consecutive patients who met the inclusion/exclusion criteria (see Appendix A) participated in this study. They were recruited from the outpatient population who were making routine follow-up visits to our movement disorder clinic. They were right-handed, non-demented, English speaking individuals with the clinical diagnosis of IPD and self-reported and clinically-observed speech impairments. Participation was voluntary.
2.2. Testing Procedures
The subjects were given placebo or apomorphine (a nonergot dopamine agonist) injections 0.05 mg/kg subcutaneously, during two consecutive outpatient visits. They were pretreated with domperidone for 48 hours, and were tested off their parkinsonian medication for 12 hours. The Mini-Mental State Examination (MMSE) [17] was administered before the injection on the first visit. Speech tasks were carried out at baseline (prior to injection) and 30 minutes post injection [14, 15]. Subjects' performance on other non-speech motor tasks were rated using the motor section of the Unified Parkinson’s Disease Rating Scale (MUPDRS) [18].

2.3. Stimuli Design
The speech samples included four repetitions of maximum sustained vowel phonations (MSVPs) of /a/, and four repetitions of comfortable vowel phonations (CVPs) of /a/ [19].

2.4. Instrumentation and Acoustic Analysis Procedures
Speech signals were recorded in a quite room on a digital audio tape deck (Sony 60ES) using a SHURE headset directional microphone with a mouth-microphone distance of 5 cm and a preamp (Symetrics). Maximum vocal intensity was measured with a digital sound level meter (Radio Shack 33-2055) placed on a tripod with a mouth-microphone distance of 50 cm. Vowel duration was measured with a digital stop-watch. The signals was later digitized into the Computerized Speech Lab (CSL, Kay Elemetrics Corp.) using a sampling rate of 25 kHz. For each of the MSVPs, two 2-second samples were selected, one from the beginning, one from the ending of each production. However, to find the most stable production, the first and the last three-thirds of each MSVP were excluded from the sample selection. For the CVPs, only one 2-second sample was selected in the middle of each production. The vocal parameters analyzed were Fundamental frequency (F0, Hz), Jitter (%), Fundamental frequency variation (vF0, %), Shimmer (dB), and Harmonic/noise ratio (dB) (Multi-Dimensional Voice Program, Model 4305, Kay Elemetrics Corp.).

2.5. Speech Impairment Ratings
For each subject, an overall speech impairment score was obtained at baseline on the first-day visit based on a conversational speech sample. The rating scale is a 5-point scale for impairment ranging from none (0), mild (1), mild-moderate (2), moderate (3) to severe (4). The rating was done by one of the experimenters who was a speech-language pathologist and a speech scientist.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Duration of PD (year)</th>
<th>Hoehn &amp; Yahr (off)</th>
<th>MMSE score (30)</th>
<th>Speech impairment rating (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>72</td>
<td>9</td>
<td>3</td>
<td>30</td>
<td>mild (1)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>70</td>
<td>21</td>
<td>4</td>
<td>30</td>
<td>moderate (3)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>83</td>
<td>3</td>
<td>3</td>
<td>30</td>
<td>mild (1)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>70</td>
<td>3</td>
<td>3</td>
<td>29</td>
<td>mild-moderate (2)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>68</td>
<td>14</td>
<td>3</td>
<td>28</td>
<td>mild-moderate (2)</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>63</td>
<td>7</td>
<td>2</td>
<td>30</td>
<td>mild (1)</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>70</td>
<td>4</td>
<td>3</td>
<td>29</td>
<td>mild (1)</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>83</td>
<td>4</td>
<td>3</td>
<td>26</td>
<td>moderate (3)</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>78</td>
<td>16</td>
<td>3</td>
<td>24</td>
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</tr>
<tr>
<td>10</td>
<td>M</td>
<td>76</td>
<td>6</td>
<td>3</td>
<td>28</td>
<td>mild-moderate (2)</td>
</tr>
</tbody>
</table>

Mean: 73.3 (6.5) 8.7 (6.25) 3 (0.47) 28.4 (2.01)

Table 1. Subject information, the MMSE scores and speech impairment scores

2.6. Statistical Analyses
A two-factor ANOVA with repeated measures was used to assess the significance of the changes in vocal parameters across the experimental conditions. The independent variables were treatment (medication vs. placebo), and session (baseline vs. post-injection). The dependent variables were the five vocal parameters described above.

3. RESULTS
Subject information, the MMSE and speech impairment scores were summarized in Table 1. The severity of the speech impairment in the subjects ranged from mild to moderate. The subjective rating scores reported here are highly correlated with the speech intelligibility scores from the sentence test of the AIDS [13] that have been previously reported [14, 15]. It is clear that the speech impairment scores do not correlate with the duration of the disease which suggests the variability in speech impairment in this patient population.

The mean values of the acoustically analyzed vocal parameters of MSVPs and CVPs are presented in Table 2 and Table 3, respectively. It is clear from the results that none of the measured vocal parameters improved or worsened significantly as a result of the administration of apomorphine. A two-factor ANOVA with repeated measures was used to assess the significance of the changes in vocal parameters across the experimental conditions. The following results were obtained.

First, the baseline values were not significantly different from each other for any of the vocal parameters, indicating that the subjects’ conditions were stable across the two testing days. Second, no statistically significant differences were found between the two main factors or on their interactions on any of the vocal parameters. Third, for any of the vocal parameters, no significant differences were found between the two samples, one from the earlier portion, and one from the later portion of each of the MSVPs. This finding indicates that the within-sample variations for sustained phonations of vowel /a/ are relatively small for IPD patients with mild to moderate speech impairment. However, as we have previously reported, the non-speech motor performance in these patients did improve significantly as measured by the MUPDRS. The mean change in MUPDRS on the placebo day was 5.6 (sd. 8.12) and on the apomorphine day was 11.25 (sd. 8.2). These changes were statistically significant (p=.0078) by Wilcoxon sign rank test.
4. DISCUSSION

While none of the vocal parameters were improved or worsened as a result of the central dopaminergic stimulation, the mean vocal intensity was slightly higher for the MSVPs than the CVPs under the apomorphine condition. The subjects were aware from the instructions that they were required to sustain the vowel as long as they could when producing MSVPs, but not required to do so when producing CVPs. Thus, a conscious effort by the subjects might have contributed to the small difference in these results. In fact, when this conscious effort is combined with therapeutic training, PD patients showed significant improvement in their speech functions [20].

A previous study on acoustic voice analysis in patients with PD treated with dopaminergic medications using identical analyzing programs has reported increased mean F0 (180.1 Hz, sd. = 41.8 Hz) in the treated male PD patients [21]. Such a trend was not observed in this study under the post-apomorphine condition for the male subjects (see Table 2 and Table 3). More F0 variations were noted, however, under the experimental condition with four of the five subjects with a speech impairment rating greater than mild. Thus, it is possible that elevated F0 or varied F0 in male PD patients may not be a response to the dopaminergic stimulation, but rather, a part of the dysarthric symptom complex.

It is clear from the results presented above that under a double-blind, placebo controlled design, central dopaminergic stimulation by apomorphine administration improved non-speech parkinsonism in this series of patients, as judged by change in MUPDRS, while it failed to affect any of the selected vocal parameters. This finding is consistent with some recent studies examining effects of levodopa on finger and articulatory movement in Parkinson's disease [22]. While all the nine patients in that study demonstrated improvement in finger forces, none showed any positive changes in forces of articulatory movement.

It is known that treatment of PD with levodopa is effective in addressing symptoms that result predominantly from lesions of the nigro-striatal dopaminergic system (bradykinesia or akinesia, rigidity, and tremor) [7]. Dysarthria or speech impairment seen in PD, on the other hand, has been shown to be strongly correlated with axial symptoms such as cognitive impairment and gait disorder. None of which showed significant response to levodopa treatment [23]. It is noteworthy that in a study examining effects of central dopaminergic stimulation by apomorphine on swallowing disorders (SD) in Parkinson's disease, the improvement of total swallowing duration (TSD) was noted in five of the eight patients examined. Further, the improvement was correlated with the voluntary motoricity of the buccolingualfacial motor score as defined by alternate lip, tongue and jaw movements [24]. Together, these results suggest that non-dopaminergic lesions may be responsible for speech impairment in PD.

Future studies should focus on non-dopaminergic lesions and their effect on speech production as well as responses in speech mechanisms to pharmacological treatment of the nondopaminergic receptors in PD.

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APPENDIX

A. Inclusion/Exclusion Criteria

Inclusion: 1. Clinical diagnosis of PD, stages 3 and 4 "off" [16]  
2. Levodopa responsiveness
3. MMSE > 24
4. No active hallucinations or delusions
5. Hamilton depression scale score < 15
6. Native English speaking

Exclusion: 1. Clinical diagnosis of non-IPD parkinsonism
2. Lack of levodopa responsiveness
3. MMSE < 24
4. Active hallucinations or delusions
5. Hamilton depression scale score < 15
6. Presence of trunkal or linguo-buccal dyskinesias

REFERENCES
