

Critical Review: Does treatment with levodopa improve swallowing function in patients with Parkinson's Disease?

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This critical review examines the evidence regarding the effects of levodopa on the swallowing function of persons with Parkinson's disease in seven studies. Study designs include: mixed design, single and counterbalancing repeated measures pre-posttest designs, critical reviews, systematic review and meta-analysis. Overall, research supporting the ability of levodopa to improve swallowing function in patients with Parkinson's disease is lacking and the findings are inconclusive. More research is required to examine this relationship. Recommendations for future research and clinical implications are provided.

Introduction

Dysphagia has been reported to be the main cause of pulmonary infection and death in patients with Parkinson's disease (PD) (Melo & Monteiro, 2012). It is present in more than 90% of PD patients and it is symptomatic in up to 50% of these patients (Hunter et al., 1997). Swallowing dysfunction in PD patients is multifactorial with abnormalities possible in all phases of swallowing (Hunter et al., 1997).

While Parkinson's disease is defined as a dopaminergic nigrostriatal disorder, not all symptoms of the disease show improvement when treated with dopamine replacement strategies (Menezes & Melo, 2009). While levodopa improves the motor symptoms of PD, symptoms such as pain, cognitive impairment, and dysautonomia do not show improvement after treatment with levodopa (Sutton, 2012). The ability of levodopa to improve swallowing function in particular is not well understood.

Professionals working in the area of clinical dysphagia need to know whether or not PD patients being treated with levodopa are at risk for aspiration due to swallowing dysfunction. This knowledge is vital given that many patients with PD and dysphagia are asymptomatic for swallowing difficulties, which makes them prone to silent aspiration (Sutton, 2012). The role of levodopa in restoring swallowing function is currently unclear in the literature, hence this study seeks to examine the evidence regarding its role in more detail.

Objectives

The primary objective of this paper is to critically evaluate existing literature regarding the impact of levodopa treatment on swallowing function

in patients with PD. The secondary objective is to provide recommendations for clinical practice and future research.

Methods

Search Strategy

Computerized databases, including CINAHL, PubMed, and PsychINFO, were searched using the following search strategy:

((Parkinson's disease) OR (parkinsonian))
AND ((swallowing) OR (dysphagia)) AND
(Levodopa).

The search was limited to articles written in English between 1989 and 2013. References from selected articles were examined to identify articles not found by electronic search.

Selection Criteria

Studies selected for inclusion in this critical review paper were required to examine the effect of levodopa on swallowing function of individuals with Parkinson's disease. The selection criteria for primary journal articles required each individual to serve as their own control by having their swallowing examined both before and after levodopa administration. No limits were set on the age, sex, etiology, stage, or severity of PD, or the demographics of research participants.

Data Collection

Results of the literature search yielded seven articles that were consistent with the selection criteria: mixed design (nonrandomized clinical trial and single repeated measures pre-posttest design) (1), single repeated measures pre-posttest designs (2), counterbalancing repeated measures design (1),

critical reviews (2), and a systematic review and meta-analysis of the literature (1).

Results

Mixed Design and Single Repeated Measure Designs

Bushmann, Dobbmeyer, Leeker and Perlmutter (1989) examined the swallowing abnormalities and their response to treatment with levodopa in 20 subjects with PD. They also compared the presence of swallowing abnormalities in patients with PD to those of healthy controls. For the purposes of this article, only the swallowing abnormalities of the patients with PD and their response to levodopa will be discussed.

Swallowing function was assessed with a modified barium swallow (MBS) both on and off levodopa, and rated by two speech-language pathologists, one of whom was blinded, using an objective protocol. Appropriate analysis using the kappa statistic revealed strong inter-rater reliability for assessment of all swallowing behaviours. Results showed abnormal swallows in 15 patients off levodopa. Of those, five showed mild to dramatic improvement (decreased residue and transit time) on levodopa, and one showed deterioration. No statistical analysis was completed on the MBS findings that were performed both before and after treatment with levodopa.

This study provided a high level of evidence (level 2b) which included experimenter blinding and interrater statistical analysis. However, there was no statistical analysis performed on the pre and post levodopa MBS findings.

Fuh et al. (1997) examined several characteristics of swallowing abnormalities in PD patients. For the purposes of this review, only the changes in swallowing function in response to levodopa treatment will be discussed.

This study included 19 patients, 5 of which had never been treated with levodopa. These 5 patients demonstrated responsiveness to levodopa during the study. Swallowing function was evaluated with an MBS, on and off levodopa. Rating was performed by one of the researchers of the study who was partially blinded and whose professional designation was not reported. The results showed that 12 of 19 PD patients had abnormal swallows on the MBS. Six of 12 patients showed improvements (oral phase, aspiration, decreased residue) after levodopa, with one of these patients showing improvement in one phase of swallowing and deterioration in another.

This study provided a relatively high level of evidence (level 2b), however no statistical analysis was performed on the 'on' levodopa MBS findings.

In addition, the rater was only partially blinded and the ratings were qualitative and subjective in nature.

Hunter, Cramer, Austin, Woodward, and Hughes (1997) examined the effects of dopaminergic stimulation on swallowing abnormalities in patients with PD. They studied the effects of oral levodopa and subcutaneous apomorphine on swallowing function separately. The effects of subcutaneous apomorphine will not be discussed in this review.

This study consisted of 15 patients with PD and predetermined symptomatic dysphagia. All patients had been taking levodopa therapy chronically. Swallowing function was evaluated using an MBS before and after levodopa, and rated objectively by two blinded speech-language pathologists. Pre-levodopa and post-levodopa swallowing variables (transit time, aspiration, penetration and vallecular pooling) were analyzed using a non-parametric Wilcoxon signed rank test. The results showed a reduction in the length of the oral preparatory phase with semisolids and thin fluids ($p < 0.05$), and an unexpected increase in the oral phase time and total initial swallow time with the solid bolus ($p < 0.05$). No statistically significant differences were found when analyzing the data at the level of the individual.

This study provided a high level of evidence (level 2b). The researchers included the use of scales and protocols to help decrease the subjectivity, and they performed statistical analysis of the MBS findings. However, only one of two rater's data was analyzed and no interrater reliability statistics were performed.

Lim, Leow, Huckabee, Frampton, and Anderson (2008) examined the effect of levodopa on swallowing and respiratory function. For the purposes of this review, only the effects of levodopa on swallowing function will be discussed.

This study consisted of 10 patients who were currently being treated with levodopa. Nasendoscopy was used to evaluate swallowing function both on and off levodopa during two sessions spaced at least a week apart. Participants were randomly allocated to two groups of 5 subjects, with group one being 'on' levodopa in the first session and 'off' levodopa in their second session, and group two being assessed in the reverse order in order to control for potential bias. One of the 10 participants did not perform the qualitative swallowing assessment due to discomfort from the endoscopy. Qualitative analysis of swallowing dysfunction examining the incidence of aspiration, penetration, residue, spillage and vocal fold bowing revealed no significant changes or trends, as analyzed by McNemar testing.

This study provided a moderately high level of evidence (level 2b), which included controlling for an order bias and performing statistical analysis of the nasendoscopy findings. However, the endoscopy ratings are qualitative in nature.

Systematic Review and Meta-analysis

Menezes and Melo (2009) selected five studies to include in their systematic review assessing the role of levodopa in swallowing function. They examined the outcomes of oral transit time and pharyngeal transit time for thin fluids and solids, and aspiration in subsets of these five studies. No single outcome measure was available to be pooled across all five studies. The researchers transformed the descriptive statistics presented in three of the studies into a mean +/- standard deviation when comparing the patients' swallowing abnormalities in the 'on' and 'off' levodopa states. Given that two of these three studies reported descriptive data only, statistical meta-analysis was limited to mean comparisons only. Their results showed that none of the dysphagia parameters evaluated in their meta-analysis demonstrated significant improvement after treatment with levodopa.

Critical Reviews

Sutton (2012) wrote a critical review paper that examined the role of levodopa in swallowing function. He supported levodopa-induced swallowing improvement by describing the relationship of dysphagia and mortality in PD patients while comparing the pre and post levodopa era, and by discussing case reports that demonstrated swallowing improvements in response to levodopa therapy. He also identified and addressed many flaws that were present in the meta-analysis performed by Menezes and Melo (2009), which included mislabeled figures, incorrect source statistics and flaws in study selection and methodology.

A critical review completed by Melo and Monteiro (2012) summarized the results of eight studies that examined swallowing function in patients with PD. Five of these studies also examined the role of levodopa in swallowing function. These five studies comprise a fair representation of the available research addressing this topic. Their review provides an overview of study results that pertain to each phase of swallowing, and concludes that there is no evidence that levodopa consistently improves swallowing.

Discussion

When examining the primary journal articles comprehensively, two of the four studies did not perform statistical analysis on any of their data relating to swallowing abnormalities observed on and off levodopa (Bushman et al., 1989; Fuh et al., 1997). Only a descriptive, qualitative, and subjective analysis of MBS results was performed. It is very difficult to draw significant conclusions that can assist with making practice decisions from studies that have not performed statistical analysis and that are at risk of subjective bias.

Statistical analysis to examine the effects of possible confounding variables such as age, sex, comorbidities, additional medications, disease severity, complaints of dysphagia symptoms, and duration of disease was not reported in any of these studies. None of the studies reported attempts to control for any of these variables, although the study by Lim et al. (2008) did report controlling for an order bias. Two of the studies examined the relationship between patient complaints of dysphagia and the presence of swallowing abnormalities on the MBS, but only when off levodopa (Bushman et al., 1989; Fuh et al., 1997). The study by Fuh et al. (1997) included patients that had never taken levodopa before, and no statistical analysis was performed to control for this variable. None of the studies examined the chronic effects of levodopa on swallowing and the length of time that each patient had been previously taking levodopa was not controlled for. These two variables may have a significant impact on the effects that levodopa has on swallowing function, and they should be examined and controlled for in further research.

The study by Bushmann et al. (1989) was the only study to perform statistical analysis on interrater reliability, and present data from two independent raters. Fuh et al. (1997) chose to eliminate the data collected from one of their MBS raters without presenting a thorough explanation, which introduces a source of bias. Blinding occurred fully in two studies (Bushman et al., 1989; Hunter et al., 1997), partially in another (Fuh et al, 1997), and was not discussed in the study by Lim et al. (2008). The blinding of all raters should have occurred in all studies as it is feasible and serves to eliminate rater bias. The professional designation, and hence qualification of the raters was clear in only two of the studies reviewed (Bushman et al., 1989; Hunter et al., 1997). Using qualified raters strengthens the level of evidence that a study provides.

The variability in levodopa dose amongst the studies is concerning. Some of the studies had patients take 'their regular amount' of levodopa

(Bushmann et al., 1989; Lim et al., 2008), while others used a fixed amount of levodopa (Fuh et al., 1997; Hunter et al., 1997). A fixed dosage is easier to examine statistically in order to control for dosage effects. Further research using a fixed amount of levodopa would allow for more appropriate comparisons amongst studies and stronger conclusive evidence.

The reviewed studies often examined different swallowing behaviour measures. This made it difficult to compare outcomes from one study to another. Pharyngeal residue and aspiration were the only two measures found to be common amongst all of the studies. This is largely due to the fact that one of the studies used a nasendoscope instead of an MBS to examine patients' swallowing. The nasendoscope does not allow for visualization of the oral preparatory or oral phase, the swallow initiation, or the esophageal phase whereas an MBS does. The nasendoscope is however, more efficient at detecting penetration and aspiration than the MBS (Singh et al., 2009). In addition, none of the studies examined the esophageal phase of swallowing, however, abnormal esophageal peristalsis and gastric reflux are commonly observed swallowing abnormalities in patients with PD (Edwards, Quigley & Pfeiffer, 1992; Stroudley & Walsh, 1991).

The sample sizes used in all studies were relatively small; a larger number of subjects may have assisted with identifying meaningful results and achieving statistical significance. All of these studies used a study design that results in a relatively high level of evidence (level 2b). These studies did not use a randomized control trial, which is the gold standard, likely due to the fact that this design is not realistic for this type of study as it is unethical to withhold levodopa medication from PD patients. Further methodological flaws in these studies diminish the level of evidence that they provide. As previously discussed, these studies were descriptive in nature, they often did not control for confounding variables, and statistical analysis was not performed in all studies. The results of these studies must therefore be interpreted with caution when attempting to draw causal conclusions.

When evaluating the meta-analysis and the critical reviews, many weaknesses limit the clinical usefulness of their conclusions. The majority of the statistical comparisons in the meta-analysis performed by Menezes and Melo (2009) were performed on only two studies, which limits the comprehensiveness of this review. In addition, one of the included studies used healthy individuals as controls, while the remaining studies the individuals with PD served as their own controls. This makes their comparisons and analyses less appropriate and

applicable to clinical practice. The small number of included studies and measured parameters, and the minimal statistics available to analyze limits the clinical usefulness of the results of this meta-analysis. When examining the critical reviews, Sutton's (2012) overall conclusion suggesting that dysphagia is responsive to levodopa lacks research-based evidence and is largely anecdotal. He claims that recent pilot studies, referring to the studies reviewed in this review and in the meta-analysis performed by Menezes and Melo (2009), neither strengthen nor weaken his point of view. However, these 'pilot studies' are the only experimental studies available in the literature. The evidence that he refers to involves observations and case studies only. This implies that his point of view is based on observations and nonexperimental studies only, which do not hold a lot of merit in the scientific community. In the critical review produced by Melo and Monteiro (2012), there is little, if any, critiquing of the studies or comprehensive analysis that brings the study results together. It would have been beneficial for this review to have included a thorough critique of each study's results, as opposed to just stating the results of each study.

Conclusions

In summary, research support for levodopa-induced swallowing improvement in patients with PD is lacking and the overall findings are inconclusive. Two of the reviewed studies showed qualitative improvements in swallowing function in up to fifty percent of PD patients with swallowing abnormalities, suggesting an individualized benefit from taking levodopa. However, these studies did not perform any statistical analyses which diminishes the validity of their results. The other two reviewed studies showed limited significant changes. Some of the significant changes found in these studies actually demonstrated a deterioration in swallowing after levodopa administration. In addition, the critical reviews and meta-analysis provide conflicting results. While an individual benefit of levodopa on swallowing function is possible, more studies involving quantitative research and statistical analysis are needed to resolve the conflicting findings in the literature.

Recommendations

Future research should focus on the following in order to provide more compelling evidence:

- Collecting more quantitative data as opposed to using only descriptive subjective

findings in order to strengthen the validity of the evidence.

- Performing appropriate statistical analysis on research findings both pre and post levodopa administration.
- Controlling for possible confounding variables through statistical analysis or methodological adjustments.
- Using two or more qualified blinded raters, presenting the data from all raters, and performing interrater statistical analysis to control for subjective biases.
- Performing studies using a fixed amount of levodopa for all subjects to allow for more appropriate comparisons across studies.
- Performing studies that examine the chronic effects of levodopa on swallowing function, as opposed to only the short-term effects.
- Using larger sample sizes to assist with the identification of more meaningful results.
- Examining similar swallowing behaviour measures to those examined in existing studies to allow for comparison across studies.
- Examining the effects of levodopa on the esophageal stage of swallowing.

Clinical Implications

The conflicting results of these reviewed studies suggest that clinicians should exercise caution when implementing study results to their clinical practice. The findings of these studies allude to certain implications that clinicians should consider when assessing and treating dysphagia in PD patients who are taking levodopa. Firstly, it is important for clinicians to remember that the effects of levodopa on swallowing function are highly individualized. Beneficial effects from taking levodopa cannot be assumed, and some patients may actually show worsening effects after levodopa administration. Patients should be assessed as individuals with no preconceived notions regarding the effects of levodopa on their swallowing function. Secondly, it would be beneficial for clinicians to initially assess PD patients when they are both on and off their levodopa medication. This would assist with the development of a comprehensive plan for each patient's diet that accounts for any differences in their swallowing function when on or off this medication.

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