Critical Review:
Does levodopa have beneficial effects on the dysphagia in patients with Parkinson's disease?

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The current paper critically outlines research articles investigating the effects of levodopa on dysphagia in patients with Parkinson's disease. Five articles were found that met the criteria of the review. The design, methodology, participants, statistical analyses and results are discussed and critiqued for the validity of the study. A number of limitations were identified across the studies with some common themes emerging. The collective results of the studies provide mixed findings regarding the effectiveness of levodopa on dysphagia in PD.

Introduction

Research has shown that up to 50% of patients with Parkinson's disease (PD) have symptoms of dysphagia (as cited in Hunter et al, 1997) and up to 100% have abnormalities on Modified Barium Swallow (MBS) studies (as cited in Lim et al, 2008). It has further been reported that patients with PD are 6 times more likely to die of aspiration pneumonia than those without PD (Morgnate et al, 2000). Aside from dysphagia, another commonality among patients with PD is the medication prescribed for general motor symptoms of PD: levodopa. It then follows that any possible effects levodopa may have on the swallow be well understood. For Speech Language Pathologists (SLPs) working in an acute care setting, information on what may worsen or improve patients' swallows is imperative when conducting assessment and treatment planning.

Objectives

The objective of this critical review is to evaluate the existing literature available investigating the effects of levodopa on swallowing in patients with PD. This information can then be disseminated for use in the clinical setting.

Methods

Search Strategy

The search was completed using computerized databases PubMed and CINAHL. Search words used were (dysphagia or swallowing) AND (Parkinson's disease) AND (levodopa)

Selection Criteria

Any studies investigating the effects of levodopa on swallowing in PD were included in the review.

Data Collection

Based on the database searches and selection criteria, the following research papers were included in the critical review: within group repeated measures design (2), within group crossover design (1), descriptive study (1), and case study (1).

Results

Clane et al (1970) used a repeated measures design to investigate the difference in the swallow of patients with PD following levodopa versus placebo administered. Participants were 19 patients with PD and 1 patient with post-encephalitis. Eleven of the patients reported having difficulty eating. Each participant was given both levodopa and a placebo in a random order. Both participants and the radiologist were blind to the treatment schedule.

The procedure involved having patients swallow 2-3 boluses of Micropaque while standing as cineradiographic images were taken at a rate of 24 frames per second. This was completed for both levodopa and placebo conditions. The levodopa condition was defined as the maximum tolerated dose for each individual, ranging from 1-6.8 grams per day. The swallows of the 20 participants were evaluated for duration of pharyngeal deglutition in number of cine-frames (24 frames/second). This was defined as the time from the palatal closure of the nasopharynx to the relaxation of the hypopharynx (return of the epiglottis to its natural position). Only 18 of the 20 paired films were included in the timed analyses of pharyngeal deglutition. To analyze the difference between the two conditions, the researchers used a Wilcoxon sign rank test. No significant difference was found between the levodopa (22.6 frames) and a placebo (23.3 frames) conditions. General qualitative observations were also made on the pharyngeal phase of the swallow. This was reported to be normal across participants. The researchers therefore concluded that levodopa has no effect on pharyngeal deglutition in patients with PD.

This data should however be interpreted with caution as there are a number of limitations to the study. Firstly, it was unclear as to how far in advance of the swallow assessment the drugs were administered or if this was controlled. Because the effects of levodopa dissipate over time, it is important to control for the effects of time since administration. This also does not allow future researchers to replicate the study. Secondly, there were no multiple baseline or treatment measures completed for a more reliable assessment of swallowing. To make this study more comprehensive, the researchers could have looked at all phases of the swallow and analyzed the qualitative observations in a quantitative manner. This could have been done with a number of raters evaluating the swallow along a standardized rating scale. There were also a number of limitations with the participants alone. There was no power calculation reported to determine the likelihood of a Type II error occurring with the data for 18 participants. Also, as the researchers started out with 20 participants, they should have reported why data from two participants was not included as it may have affected the results. As there was one participant with post-encephalitis instead of PD, this also may have affected the results in terms of the current research question. The researchers could also have collected more complete demographic and disease severity information and analyzed swallowing and possible effects of levodopa in terms of that information (e.g. severity, length of disease).

The second repeated measures design, by Hunter et al (1997), compared the effects of levodopa and ampomorphine on swallowing in patients with PD. Participants were 15 (12 male, 3 female) patients with PD and dysphagia. Patients were recruited from a movement disorder clinic and had a mean age of 71 years and mean duration of disease of 11 years. All patients were taking levodopa and five were taking ampomorphine prior to the study.

Participants were evaluated on two mornings, one week apart. Participants were administered levodopa the first morning and apomorphine the second. Each day, participants completed an MBS having been off medication for at least 8 hours. Serial motor tasks were then done every 15 minutes after taking medications until effects of medication were observed. When stable, participants completed a second MBS. Boluses assessed in the MBS were thin liquid, jelly consistency, and toast. The same procedure was followed each day.

Two experienced SLPs were blind to the condition and evaluated the MBS images on a number of qualitative variables (i.e., aspiration, laryngeal penetration, vallecular pooling, place of swallow initiation, and mean swallows to clear pharynx) and quantitative variables (i.e., time of oral preparatory, oral, and pharyngeal phases, rapid pharyngeal transit time, total initial swallow time and complete swallow time). Qualitative measures were changed to a 4-point scale according to the percentage ratings (i.e., nil, mild = <10%, moderate = 10-39%, and severe = 40-100%). Of the qualitative measures, levodopa was only found to reduce the number of swallows to clear the solid bolus. Quantitatively, a reduction in the oral preparatory phase of the swallow was found for both the jelly consistency and thin liquids. In contrast, an increase in the oral phase of the swallow was observed for the solid consistency. No other significant changes in the swallow were observed after levodopa.

The researchers performed further analysis on the seven most abnormal quantitative results. It was again found that levodopa resulted in a reduction of the oral preparatory phase for the same consistencies. It was further identified that levodopa resulted in a reduction in rapid pharyngeal transit and pharyngeal phase time for fluids. Swallowing data was analyzed using the Wilcoxon signed rank test because of the small sample size and the abnormal distribution.

The mix of both qualitative and quantitative measures evaluated gives the researchers a more complete look at the swallow and strengths the validity of the results. To improve the validity of the results, the researchers could have blinded the participants to the type of medication taken and randomized this as well. Although it appeared that the researchers were trying to further validate their findings by analyzing the seven most abnormal timed qualities of the swallow, this seemed redundant and unnecessary. The participants of the study provided data on their disease severity and length of disease. This information could have been analyzed in terms of the relationship between disease severity and swallowing abnormalities to show a more complete picture of swallowing abnormalities in this population. The researchers did however identify the small sample size and mention the possible Type II error because of this. No power calculation was mentioned. In order for future researchers to replicate these findings, more information of the motor evaluation would be necessary and any instructions given to the raters.

In the most recent study currently being reviewed, Lim et al (2008) investigated the effects of levodopa on both swallowing and respiration. In this within group crossover design, 10 participants were recruited from a PD outpatient clinic. Only those patients with PD, taking levodopa and without a history of smoking, neurological impairments or breathing disorders were

included in the study. Individual demographic and disease information (e.g., Hoehn and Yahr stage, years with PD) was collected. Nine of the 10 participants completed all tasks with one participant finding the endoscope too uncomfortable.

Participants were required to take part in MBS studies on two mornings one week apart. Participants were randomly assigned to two groups: (1) Day 1: on medication, Day 2: off medication; (2) Day 1: off medication, Day 2: on medication. The 'off' condition consisted of patients having had no levodopa for at least 12 hours. Prior to the first session, participants completed a dysphagia questionnaire on quality of life (SWAL-QOL). During each session, participants completed a number of tasks: (1) the Unified Parkinson's Disease Rating Scale (UPDRS) sections II and III; (2)coordination of swallowing and respiration tasks with EMG face electrodes; (3) timed-test of swallowing; (4) lung function using spirometry, and; (5) qualitative assessment of swallowing with nasendoscope with a variety of consistencies. Data was analyzed using the paired t-test and the McNemar test for the parametric and nonparametric data respectively.

In terms of swallowing, the timed-test of swallowing was evaluated on 5 areas: (1) number of swallows; (2) time taken; (3) average volume per swallow; (4) average time per swallow, and; (5) swallowing capacity. The researchers found no difference in condition with a non-significant trend to decrease the volume per swallow when on levodopa. No other changes or trends in swallowing were observed between the on and off conditions for coordination of swallowing and respiration and assessment of swallowing.

The measures used to evaluate swallowing in this study allowed for both qualitative and quantitative data from three assessment tasks. Due to the nature of these tasks, researchers could have improved the design of their study by collecting multiple baseline and experimental measures as they are not as invasive as MBS studies. Multiple measures could have allowed for more reliable assessments of the swallows. Also, the researchers did not recruit patients with PD that specifically had swallowing abnormalities. If the researchers investigated this subgroup of the population specifically, the researchers may have reached a different outcome.

Another limitation of the study, prevalent in the studies being currently reviewed, is the small sample sizes. Again, no power calculation was mentioned and the researchers themselves reported that the results could be due to chance. Further information that was not reported was that of the swallowing assessment: how it was rated and the qualitative findings. This making it difficult to replicate the study. The absence of this information, the lack of participants and the poor study design reduce the validity of the evidence in this study.

Buschmann et al (1989) designed a descriptive single-blinded study. Participants were 20 patients with PD recruited from a PD Association group and a movement disorder clinic. Inclusion criteria did not include the presence of dysphagia. A control group consisted of 13 of the patients' spouses.

Patients withheld all Parkinson's medication for at least eight hours prior to test day. All participants underwent a neurological exam, rated on the Hoehn and Yahr scales, oral motor screening and a bedside dysphagia screening. A baseline MBS was then completed with a variety of bolus consistencies. Patients were then given their usual dose of levodopa and the clinical ratings were completed a second time. A second MBS was completed in the same manner as the first following patients' reports of effects of medication or after 90 minutes. Control participants only completed one MBS study.

Two raters (one blind to condition and group) evaluated the MBS studies for 18 observations (e.g., bolus formation, coating of pharyngeal wall, vellecular residue, aspiration before, during and after). Inter-rater reliability was calculated for each of the 18 observations using the kappa statistic for nominal data. Chi-squared analyses were calculated to compare groups.

For group comparisons, patients with PD were found to have significantly more complaints of dysphagia and had more abnormal swallows than controls. There was no significant relationship found between complaints of dysphagia and abnormal MBS findings. For inter-rater reliability, "substantial to almost perfect" agreement was found across the 18 observations.

Further statistical analyses were not completed, but the researchers did provide descriptive data in terms of response to levodopa. Five patients shown to have abnormal swallows demonstrated improvement after levodopa, ranging from mild to dramatic. The most recurrent changes observed after levodopa were decreased coating of the pharyngeal walls, decreased vallecular residue and, most notably, increase in transit times for thick boluses. In contrast, 1 patient showed a decline in their swallowing function following levodopa.

Following this, the researchers increased the dose of levodopa to 4 patients and were asked to return for further MBS studies. Two participants were unable to tolerate the chronically higher dose of medication. They then performed a repeat MBS after a single higher dose with no change in swallowing. In the remaining two patients, only one showed some improvement (decreased vallecular residue and normalization of laryngeal elevation).

The greatest limitation of this study is the lack of statistical analysis. Although the researchers evaluated the swallow on a large number of observations, statistical analyses of the data would have made the results more valid. A 4-point rating scale might have been developed for the raters when evaluating the MBS studies. These data could then have been statistically analyzed for a more unbiased assessment at the results. Conversely, if the researcher wished to provide a more descriptive study, more in-depth explanations of the observations could have been made.

Although no statistics were analyzed for the observations of the swallow, the small sample size may also have affected the results of the study. Also, as mentioned in critiques of previous studies, patients with dysphagia were not specifically selected. This may have resulted in different findings.

A case study was performed by Fonda, Schwarz and Clinnick (1995) to assess the effectiveness of taking levodopa one hour prior to meals on swallowing. The participant was a 72 year old male with PD (9 years post onset) and dysphagia (18 months post onset). He was on a minced diet and had lost 30 kilograms in the previous 18 months. The participant went through a biochemical screen, a chest x-ray, and a barium swallow with no abnormalities found. A MBS was then performed with liquids and solids and the swallow was assessed for total swallow time, laryngeal tremor, pooling (valleculae and pyriform), epiglottic movement, laryngeal penetration and aspiration. The MBS showed a lengthy swallowing time, vallecular pooling and aspiration of thin liquids. Following this, the participant was instructed to take his regular dose of levodopa one hour prior to meals. He was also given techniques to improve swallowing function and minimize the chance of aspiration.

The participant reported feeling his swallow had improved and the researchers confirmed this on a second MBS three weeks after instructions were given. Swallow time was reduced by 3.1 and 0.7 seconds for solids and liquids, respectively. Laryngeal tremors went from a rating of moderate/severe to mild. Laryngeal penetration of solids went from 80% to 0%. For liquids, an improvement of 100% to 25% was noted. Aspiration of liquids went from a rating of mild to nil. Assessments of facial and oral tremors were done over this time period as well and a reduction in the tremors was found after day 4 and was presumed to also contribute to the improved swallow.

The participant was followed for 2 months and his weight had increase by 6 kilograms. A few weeks after this, the participant developed pneumonia and died. The researchers concluded that the altered levodopa regiment and 'related therapy' improved swallowing function.

This study did not provide valid evidence to support levodopa taken one hour prior to meals as an effective treatment for dysphagia in patients with PD. Although the patient reported improvements in swallowing and this was shown on a MBS study, the 'related therapy' may have been the cause of this. It is unclear what was meant by this therapy aside form the techniques given to the participant to reduce aspiration. It was further unclear if the participant used these techniques during the second MBS study.

Further limitations of the study are that there was only one participant, rating of the MBS studies was not explained, and repeated measures were not taken for more valid data. Also, although the researcher suggested their intervention improved swallowing function, the participant died of pneumonia (presumed to be aspiration pneumonia) therefore the changes noted in the MBS study may not have been indicative of overall performance.

Discussion

The literature reviewed in this paper provides no conclusive evidence for the effectiveness of levodopa to improve the abnormal swallow of patients with Parkinson's disease. The majority of the articles reviewed present a set of limitations in this area of study that should be addressed in future research. The first of these limitations is the lack of repeated measures taken for more reliable data. One's swallows vary a great deal throughout a day or across days. A set of swallows within minutes may not be representative of the clients' typical swallowing performance. A number of swallows over time would allow for a more accurate illustration of the patients' swallowing function.

This, however, raises a further limitation in the assessment of swallowing. MBS studies are often used to gain a clear visual evaluation of swallowing function however the accompanied exposure to radiation is a

cause for concern for the patient. Repeated exposure to radiation would not be ethically viable and therefore repeated measures would not be possible. In this instance, researchers would be required to rely on other less invasive procedures in order to assess swallowing function.

A further limitation found across all of the reviewed articles is the small number of participants. The largest group investigated consisted of 20 participants. In none of the studies did the researchers perform power calculations to identify the likelihood of a Type II error.

Future research in this area should not only address the limitations mentioned above but also move beyond the current narrow scope of research. Researchers may want to expand this area of study to investigate how levodopa may affect other treatments of dysphagia in patients with PD such as swallowing maneuvers. Beyond dysphagia, researchers may also want to investigate the effects of levodopa on other areas of deficit and treatment such as Lee Silverman Voice Therapy. The effects of levodopa on the anatomy for speech is not well understood but would have great implications for patients with PD and associated motor speech disorders.

Clinical Implications

Although there is insufficient evidence to support the use of levodopa in reducing abnormalities in the parkinsonian swallow, the majority of the researchers noted that when examining the individual data, some participants appeared to benefit from the peak effects of levodopa when swallowing (Lim et. al., 2008; Fonda, Schwarz, Clinnick, 1995; Bushmann et. al., 1989). These researchers further suggested that clinicians may want to trial individual patients on a modified levodopa schedule as the patient may benefit and there is no detriment to the patient in doing so.

As clinicians are not involved in medication scheduling, clinicians may wish to document the timing of administration of levodopa in relation to MBS studies (i.e., assessing at peak effects or not) or other swallow assessments on an individual patient basis. The research, however, does not mandate that a change be made in the administration of levodopa for swallowing and therefore the tracking of such effects would be at the discretion of the clinician.

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