DOI: http://dx.doi.org/10.18502/cjn.v21i2.10493

Current Journal of Neurology

Original Paper

Curr J Neurol 2022; 21(2): 98-104

# The effect of pyridostigmine on post-stroke dysphagia: A randomized clinical trial

Received: 24 Nov. 2021
Accepted: 07 Feb. 2022

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**Keywords**
Stroke; Dysphagia; Pyridostigmine Bromide; Deglutition Disorders

**Abstract**

**Background:** Swallowing is one of the most complex functions of the central nervous system (CNS), which is controlled by different parts of the brain. Oropharyngeal dysphagia (OD) is one of the most common complications after stroke. Despite a variety of behavioral, compensatory, and rehabilitative methods, many stroke patients still suffer from swallowing disorders that adversely affect their quality of life (QOL). The aim of this study was to evaluate the effect of pyridostigmine on patients with post-stroke dysphagia.

**Methods:** A randomized, double-blind, placebo-controlled clinical trial was carried out on 40 patients suffering from post-stroke dysphagia. Patients were assigned randomly into two groups: intervention and control groups (20 in each group). The intervention group was treated with pyridostigmine (60 mg, three times a day, 30 minutes before each meal for three weeks), and the control group received placebo treatment in the same way. All patients (intervention and control) were evaluated according to National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Functional Communication Measures (FCM)/American Speech-Language-Hearing Association (ASHA) criteria at baseline and after three weeks of intervention. Values of $P < 0.05$ were considered statistically significant.

**Results:** In the intervention group, the mean values of NIHSS, mRS, and ASHA/FCM were significantly reduced following three weeks of treatment with pyridostigmine ($P = 0.002$, $P = 0.003$, and $P < 0.001$, respectively), but no significant differences were found in the mean NIHSS, mRS, and ASHA/FCM in the placebo group.

**Conclusion:** Although pyridogestamine is somewhat effective in post-stroke dysphagia, it has not been shown to be more important in preventing aspiration pneumonia and length of hospital stay.

**How to cite this article:** Rahimi-Jaberi A, Askari Y, Rahimi-Jaberi K, Moghadam M. The effect of pyridostigmine on post-stroke dysphagia: A randomized clinical trial. Curr J Neurol 2022; 21(2): 98-104.



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## Introduction

Stroke is the second main cause of death and the third leading cause of disability in the world.[1] More than 610000 new cases of stroke occur in the United States (US) each year, with ischemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) which are 87%, 10%, and 3%, respectively.[2] Swallowing is one of the most complex functions of the central nervous system (CNS), which is controlled by various parts of the brain, including the brainstem, limbic system, cerebellum, and motor and sensory cortex.[3] Oropharyngeal dysphagia (OD) is one of the most prevalent post-stroke complications that occurs in approximately 45% of hospitalized patients.[4] OD is the impaired transfer of a bolus from the mouth to the esophagus and can be described as a feeling of morsel stuck in the throat. Other rife complaints in these patients include coughing, suffocation, runny mouth, and feeling of food returning when swallowing solid and liquid foods.[5] Although for most this is a self-limiting occurrence, in 11% to 50% of cases, symptoms continue for up to 6 months after a stroke.[6,7] This complication enhances the likelihood of aspiration pneumonia, malnutrition, airway obstruction, and dehydration and can increase the hospitalization period, as well as, the risk of disability and mortality.[8] Individuals with dysphagia are three times more likely to develop pneumonia than other patients, increasing to 11 times if there is aspiration.[9] Despite a wide range of therapies including behavioral and compensatory therapies (such as diet modification, proper nutritional position, etc.)[10,11] and rehabilitation therapies (such as muscle training, motor control, and sensory stimulation),[12-14] many of survivors still suffer from dysphagia disorders that adversely affect their quality of life (QOL).[15] Pyridostigmine is a reversible acetylcholinesterase inhibitor,[16] which has been widely used in the symptomatic treatment of myasthenia gravis (MG).[17] Pyridostigmine is used to treat muscle weakness and bulbar symptoms (dysphagia, dysarthria, and fatigue from chewing) in people with MG rather than ocular manifestations (such as ptosis and diplopia).[18] It is also used to end the effects of neuromuscular blocking medication during anesthesia and treat organophosphate poisoning.[19] Pyridostigmine increases esophageal motility and improves manometric function in healthy individuals.[20] Although extensive research has been conducted on the diagnosis of dysphagia in patients with acute stroke and prevention of aspiration pneumonia, no targeted research has been performed to investigate the effects of drugs on dysphagia in these patients. The aim of the present study was to evaluate the effects of pyridostigmine on patients with post-stroke dysphagia and also evaluate the effectiveness of this drug on reducing the chances of aspiration pneumonia in these patients.

## Materials and Methods

***Design and study group:*** The study was designed as a randomized, double-blind, placebo-controlled clinical trial. Following ethical approval from the Medical Ethics Board of Shiraz University of Medical Sciences, Shiraz, Iran (Approval ID: IR.SUMS.REC.1398.099), patients in the stroke ward of Namazi Hospital in Shiraz who met the inclusion criteria were recruited in this study on non-probability simple convenient sampling. All patients who wished to participate in the study signed a written consent form. The randomization procedure took place after the baseline examination was completed and eligibility was determined. Forty patients who met inclusion criteria were allocated into two groups based on permuted block randomization: intervention group (n = 20) and control group (n = 20). Patients ≥ 18 years with ischemic stroke confirmed by brain imaging [computed tomography (CT) scan or magnetic resonance imaging (MRI)] who complained of difficulty swallowing, inability to swallow medication, or feeling suffocated while swallowing and obtained level 5 or lower in the American Speech-Language-Hearing Association (ASHA)/Functional Communication Measures (FCM) assessment for OD were included. Due to the side effects of pyridostigmine, the patients with pre-stroke dysphagia and patients with a history of lung disease, gastrointestinal (GI) disease, and cardiac arrhythmias were excluded from the study.

***Outcome measurements and data collection:*** Before the intervention, patient information was collected using a checklist. The checklist had three parts: the first part included demographic information (such as age and sex). The second part included patients' clinical information [history of diabetes, hypertension (HTN), coronary artery disease (CAD), stroke, the National Institutes of Health Stroke Scale (NIHSS), and the modified Rankin Scale (mRS)] at the time of hospitalization and discharge. In the third part, the FCM scale from the ASHA (2012) (ASHA/FCM) was used to measure and record complaints of swallowing

disorders in terms of OD. The NIHSS is a tool used to objectively quantify the impairment caused by a stroke. It is worthwhile in predicting the long-term consequences and prognosis of stroke.[21,22] This scale has very good sensitivity, specificity, and accuracy in predicting the consequences of stroke over a three-month period.[23] The NIHSS is composed of 11 items, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates a normal function in that specific ability, while a higher score is indicative of some levels of impairment. These items include level of consciousness, horizontal eye movement, visual field test, facial palsy, motor arm, motor leg, limb ataxia, sensory, language, speech, and extinction and inattention. The individual scores of each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being 0.[24] The mRS is a common scale used for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability.[25] Scores on this scale range from 0 (no symptoms) to 6 (dead). The ASHA/FCM is a quality scale that describes various aspects related to swallowing ability that can be evaluated during the course of speech therapy intervention and consists of 7 levels, ranging from the inability to swallow (level 1) to full oral feeding ability (level 7).[26] Clinical symptoms (such as fever, cough, pleuritic chest pain, and dyspnea) and radiological findings were also assessed for pneumonia.

***Interventions:*** Patients in the intervention group received pyridostigmine 60 mg, three times a day, 30 minutes before each meal. For patients in the control group, placebo at a dose of 60 mg, three times a day, 30 minutes before each meal was prescribed orally. All patients (intervention and control) were re-evaluated for outcome measures three weeks after discharge.

Collected data were analyzed using the SPSS software (version 20.0, IBM Corporation, Armonk, NY, USA). Data were presented as the frequencies, mean, standard deviation (SD), 95% confidence interval (CI) of the mean differences, and odds ratio (OR) with 95% CI for qualitative and quantitative variables. The chi-square test, paired t-test, and one-way analysis of variance (ANOVA) were used. Besides, logistic regression was used to evaluate the effect of the drug on dysphagia.

To compare groups in terms of quantitative data, independent t-test and Mann-Whitney U test were used. The chi-square test and the likelihood ratio were used to compare the groups in relation to the qualitative data. To compare the results over time, within each group, paired t-test and the Wilcoxon test were used. For all the statistical analyses, the significance level was set at $P < 0.05$.

## Results

The present study was performed to evaluate the effects of pyridostigmine on dysphagia in patients with ischemic stroke. 40 patients participated in this study and randomly allocated into two groups. 20 of them received pyridostigmine and 20 took the placebo. The mean age of the participants was 72.00 ± 12.06 (range: 51-90) years. 57.5% of participants were women (n = 23) and 42.5% were men (n = 17). The mean duration of hospitalization was 12.75 ± 6.20 days (3-21 days). Demographic characteristics of participants by sex are shown in table 1. The frequency distribution of demographic and clinical variables based on the type of treatment is shown in table 2.

**Table 1.** Demographic and clinical variables by gender

| Variables | Women | Men | P |
|---|---|---|---|
| Age (year) | 72.78 ± 12.71 | 70.94 ± 11.42 | 0.630 |
| ≤ 65 | 8 (34.8) | 6 (35.3) | 0.900 |
| > 65 | 15 (65.2) | 11 (64.7) | |
| Hospitalization duration (day) | 11.74 ± 5.49 | 15.74 ± 6.19 | 0.051 |
| DM | 12 (52.2) | 5 (29.4) | 0.150 |
| HTN | 20 (87.0) | 6 (35.3) | 0.001 |
| IHD | 12 (52.2) | 10 (58.8) | 0.670 |
| CVA | 3 (13.0) | 4 (23.5) | 0.380 |

Data are reported as number (percentage) for qualitative variables and mean ± standard deviation (SD) for quantitative variables

DM: Diabetes mellitus; HTN: Hypertension; IHD: Ischemic heart disease; CVA: Cerebrovascular accident

Table 3 shows the mean differences between NIHSS, mRS, and FCM/ASHA at the baseline and three weeks after treatment with the pyridostigmine and placebo.

The results showed that the mean NIHSS and mRS were significantly decreased three weeks after treatment with pyridostigmine ($P = 0.002$ and $P = 0.003$, respectively). The mean NIHSS and mRS decreased in the control group, but the differences were not statistically significant. Interestingly, a statistically significant decrease was found in both groups in terms of FCM/ASHA after three weeks taking pyridostigmine ($P < 0.001$) and placebo ($P = 0.003$).

**Table 2.** Demographic and clinical variables by type of treatment

| Variables | Intervention group (n = 20) | Control group (n = 20) | P |
|---|---|---|---|
| Age (year) | 69.80 ± 10.42 | 74.20 ± 13.41 | 0.250 |
| Age category (year) | | | |
| ≤ 65 | 9 (45.0) | 5 (25.0) | 0.180 |
| > 65 | 11 (55.0) | 15 (75.0) | |
| Sex | | | |
| Women | 11 (55.0) | 12 (60.0) | 0.740 |
| Men | 9 (45.0) | 8 (40.0) | |
| Hospitalization duration (day) | 12.55 ± 6.22 | 14.10 ± 5.84 | 0.420 |
| DM | 8 (40.0) | 9 (45.0) | 0.720 |
| HTN | 15 (75.0) | 11 (55.0) | 0.160 |
| IHD | 12 (60.0) | 7 (35.0) | 0.110 |
| CVA | 0 (0) | 7 (35.0) | 0.004 |
| Lung inflammation | | | |
| Yes | 8 (40.0) | 9 (45.0) | 0.340 |
| No | 12 (60.0) | 11 (55.0) | |
| Circulation | | | |
| Anterior | 13 (65.0) | 15 (75.0) | 0.490 |
| Posterior | 7 (35.0) | 5 (25.0) | |

Data are reported as number (percentage) for qualitative variables and mean ± standard deviation (SD) for quantitative variables

DM: Diabetes mellitus; HTN: Hypertension; IHD: Ischemic heart disease; CVA: Cerebrovascular accident

The mean difference between the NIHSS, mRS, and FCM/ASHA at the baseline and three weeks after treatment based on gender and age group is shown in table 4.

According to the results of table 5, the mean difference of NIHSS, mRS, and FCM/ASHA based on anterior circulation and posterior circulation, three weeks after treatment in the treatment group with pyridostigmine was statistically significant compared with placebo group.

## Discussion

Stroke is one of the most frequent causes of neurological swallowing disorder.[27,28] Swallowing disorder, as one of the disorders associated with stroke patients, has a relatively high prevalence and if not evaluated and treated early in the patient, it can lead to dangerous complications such as aspiration, lung infection, and sometimes death of the patient.

Most of the intervention options in the treatment of dysphagia in stroke patients have included nutritional interventions[29,30] and general dysphagia treatment programs.[31,32] Other evaluated therapies, such as thermal or olfactory stimulation[33] and medication,[34] which are primarily intended to improve the physiological aspects of swallowing, are considered experimental and are not yet routinely used.

According to the results of the present study, the mean NIHSS and mean mRS were significantly reduced three weeks after treatment with pyridostigmine, but the observed decrease in the placebo group was not statistically significant.

**Table 3.** Mean difference between National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Functional Communication Measures/American Speech-Language-Hearing Association (FCM/ASHA) before and after three weeks of treatment

| Variables | | Pyridostigmine Mean ± SD | P | Placebo Mean ± SD | P |
|---|---|---|---|---|---|
| NIHSS | Baseline | 13.00 ± 4.67 | 0.002 | 12.45 ± 5.00 | 0.069 |
| | After treatment | 10.60 ± 4.58 | | 11.90 ± 5.11 | |
| MRS | Baseline | 4.90 ± 0.55 | 0.003 | 4.80 ± 0.61 | 0.083 |
| | After treatment | 3.90 ± 1.29 | | 4.50 ± 0.82 | |
| ASHA/FCM | Baseline | 4.55 ± 0.68 | < 0.001 | 4.75 ± 0.71 | 0.003 |
| | After treatment | 2.75 ± 1.37 | | 3.55 ± 1.31 | |

NIHSS: National Institutes of Health Stroke Scale; MRS: Modified Rankin Scale; FCM: Functional Communication Measures; ASHA: American Speech-Language-Hearing Association; SD: Standard deviation

**Table 4.** The mean difference between the National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Functional Communication Measures/American Speech-Language-Hearing Association (FCM/ASHA) at the baseline and three weeks after treatment based on gender and age group

| Variables | | | Pyridostigmine | | P | Placebo | | P |
|---|---|---|---|---|---|---|---|---|
| | | | Baseline (Mean ± SD) | After treatment (Mean ± SD) | | Baseline (Mean ± SD) | After treatment (Mean ± SD) | |
| NIHSS | Sex | Women | 14.55 ± 3.90 | 11.73 ± 3.46 | < 0.050 | 12.33 ± 5.48 | 11.83 ± 5.68 | NS |
| | | Men | 11.20 ± 5.06 | 9.22 ± 5.80 | < 0.050 | 12.63 ± 4.53 | 12.00 ± 4.50 | NS |
| | Age (year) | ≤ 65 | 13.22 ± 6.11 | 9.89 ± 5.27 | < 0.050 | 11.00 ± 2.64 | 9.20 ± 1.17 | NS |
| | | > 65 | 12.82 ± 3.40 | 11.18 ± 4.35 | < 0.050 | 12.93 ± 5.56 | 12.80 ± 5.58 | NS |
| MRS | Sex | Women | 5.09 ± 0.53 | 4.00 ± 1.34 | < 0.050 | 4.92 ± 0.66 | 4.67 ± 0.67 | NS |
| | | Men | 4.67 ± 0.50 | 3.78 ± 1.30 | NS | 4.63 ± 0.51 | 4.25 ± 1.01 | NS |
| | Age (year) | ≤ 65 | 4.89 ± 0.78 | 4.00 ± 1.11 | < 0.050 | 4.40 ± 0.54 | 4.20 ± 0.43 | NS |
| | | > 65 | 4.91 ± 0.30 | 3.82 ± 1.47 | NS | 4.93 ± 0.59 | 4.60 ± 0.91 | NS |
| FCM/ASHA | Sex | Women | 4.64 ± 0.67 | 2.36 ± 1.37 | < 0.001 | 4.58 ± 0.90 | 3.67 ± 1.15 | NS |
| | | Men | 4.44 ± 0.72 | 3.22 ± 1.30 | NS | 5.00 ± 0.64 | 4.12 ± 1.59 | NS |
| | Age (year) | ≤ 65 | 4.78 ± 0.66 | 3.32 ± 1.48 | < 0.050 | 4.42 ± 0.74 | 3.20 ± 0.44 | NS |
| | | > 65 | 4.36 ± 0.67 | 2.36 ± 1.20 | < 0.050 | 4.67 ± 0.81 | 4.00 ± 1.19 | NS |

NIHSS: National Institutes of Health Stroke Scale; MRS: Modified Rankin Scale; FCM: Functional Communication Measures; ASHA: American Speech-Language-Hearing Association; SD: Standard deviation; NS: Not significant

Pyridostigmine is a reversible cholinesterase inhibitor, which does not pass through the blood-brain barrier (BBB). Inhibition of acetylcholinesterase enhances neuromuscular transmission; therefore, it prolongs the effects of acetylcholine at the neuromuscular junction.[35] In this study, the parameters related to muscle strength in the NIHSS criteria showed greater improvement than other parameters in the intervention group, which could be due to increased levels of acetylcholine at the neuromuscular junction.

Normal swallowing consists of three stages: oral, pharyngeal, and esophageal. Post-stroke dysphagia is related to the extent and location of the lesion in the brain. Lesions of the right hemisphere interfere with the pharyngeal stage of swallowing, while lesions of the left side cause oropharyngeal dysfunction. The lesion in the inferior tentorial reduces the efferent inputs to the larynx, facial muscles, and soft palate associated with swallowing.[36]

Previous studies have shown that the cholinergic nerve controls the rate of esophageal smooth muscle contraction, and regulates it in coordination with nitric oxide.[37,38]

In another study, the effects of fluoxetine, bethanechol, and pyridostigmine on healthy volunteers were studied and it was shown that these drugs could improve esophageal motility, of which pyridostigmine was more effective than other drugs.[20]

In a case study, Lee et al. reported that less than two months of treatment with pyridostigmine did not reduce dysphagia in a patient with Guillain-Barré syndrome (GBS). However, on day 75 after taking the pyridostigmine, an improvement in dysphagia was observed. The researchers claimed that pyridostigmine could improve dysphagia.[39]

ASHA/FCM was significantly decreased in the intervention group of our study, which was greater than the placebo group three weeks after pyridostigmine treatment. In addition, this reduction was greater in cases with posterior circulation strokes treated with pyridostigmine rather than in the cases with anterior circulation stroke.

**Table 5.** Mean difference between National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), and Functional Communication Measures/American Speech-Language-Hearing Association (FCM/ASHA) three weeks after intervention based on circulation

| Variable | | Pyridostigmine | P | Placebo | P |
|---|---|---|---|---|---|
| | | Mean ± SD | | Mean ± SD | |
| NIHSS | Anterior circulation | 13.23 ± 2.58 | < 0.001 | 12.27 ± 5.57 | NS |
| | Posterior circulation | 5.71 ± 3.72 | | 10.80 ± 3.70 | |
| MRS | Anterior circulation | 4.62 ± 0.87 | < 0.001 | 4.67 ± 0.61 | NS |
| | Posterior circulation | 2.57 ± 0.78 | | 4.00 ± 1.22 | |
| FCM/ASHA | Anterior circulation | 3.15 ± 1.40 | < 0.050 | 3.67 ± 1.17 | NS |
| | Posterior circulation | 2.00 ± 1.00 | | 3.20 ± 1.78 | |

NIHSS: National Institutes of Health Stroke Scale; MRS: Modified Rankin Scale; FCM: Functional Communication Measures; ASHA: American Speech-Language-Hearing Association; SD: Standard deviation; NS: Not significant

Aydogdu et al. examined the effect of pyridostigmine on dysphagia in a patient with Wallenberg syndrome who did not respond to speech therapy one month after a stroke. After receiving the pyridostigmine, facilitation in the opening of the upper esophageal valve and increased motility of the esophageal smooth muscle were observed on video fluoroscopy. It seems that pyridostigmine has a greater effect on the pharyngeal and esophageal phases of swallowing, which are under control of the premotor neurons of the ambiguous nucleus and their bilateral communication with the nucleus tractus solitarius and cranial nerves associated with swallowing.[40] In the current study, there was no significant difference in terms of the incidence of aspiration pneumonia between pyridostigmine and placebo groups, which could be attributed to increased salivation in patients receiving pyridostigmine. It may be possible to reduce this complication by reducing the dose of pyridostigmine.

In the present study, some limitations are acknowledged, such as the small sample size. However, it seems that having a placebo treatment as a control group and an equal number of samples of the two groups reduced the bias.

## Conclusion

Three weeks of treatment with pyridostigmine reduced NIHSS, mRS, and FCM/ASHA in patients with stroke. Although pyridostigmine is somewhat effective in post-stroke dysphagia, it has not been shown to be more important in preventing aspiration pneumonia and length of hospital stay. Therefore, a study with a larger statistical population is recommended to find patients with posterior circulation stroke.

## Conflict of Interests

The authors declare no conflict of interest in this study.

## Acknowledgments

We appreciate the funding provided by the Clinical Neurology Research Center, Department of Neurology, Shiraz University of Medical Sciences and the assistance of all people in conducting this study.

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (Approval ID: IR.SUMS.REC.1398.099).

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