Effects of Fluoxetine on Poststroke Dysphagia: A Clinical Retrospective Study

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Background: To investigate whether fluoxetine improves poststroke dysphagia and to detect the potential relationship between serum brain-derived neurotrophic factor (BDNF) levels and fluoxetine effects. *Methods:* In this retrospective study, 159 stroke patients who met our study criteria were included. In total, 110 patients were placed in the control group, and 49 patients were placed in the fluoxetine group. Demographic and clinical characteristics of the patients were collected for the baseline assessment. Functional independence measure scores and American speech-language-hearing association/functional communication measures scores for swallowing were collected to evaluate the patients' swallowing function. Patients' serums were collected at weeks 1 and 3 after admission, and serum BDNF levels were measured by enzyme-linked immunosorbent assay. *T* test, chi-squared test, and general linear model analysis were performed to determine the differences between the two groups. *Results:* A significantly higher improvement of swallowing function was observed in the fluoxetine group compared with that of the control group ($P = .023$). In addition, a general linear model analysis showed that the treatment of fluoxetine has a statistically significant effect on swallowing improvement after adjustment of swallowing score on admission, stroke types, and interval between the onset of stroke and admission ($P = .022$, $R^2 = .46$, adjusted $R^2 = .446$). There is no significant difference in the change of serum BDNF levels in the two groups ($P = .269$). *Conclusions:* This study suggests that treatment with fluoxetine in stroke patients with dysphagia may improve swallowing function. A placebo-controlled, randomized clinical trial is warranted to confirm this finding.

Key Words: Poststroke—dysphagia—fluoxetine—brain-derived neurotrophic factor (BDNF)—swallowing recovery

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Introduction

Poststroke dysphagia (PSD), a common disorder in swallowing after stroke, occurs in 37%-78% of stroke patients.[1] PSD increases the risk of aspiration pneumonia, airway obstruction, malnutrition, and dehydration, resulting in increased morbidity and mortality.[2] Despite the current availability of behavioral, compensatory (such as postural adjustments, diet modification, using adaptive equipment, etc.), and rehabilitative therapies (such as muscle exercises, motion exercises, and sensory improvement), many stroke patients continue to experience significant impairments in swallowing, which impedes functional recovery progress and affects quality of life.[3,4]

Currently, there are no effective pharmacological therapies for PSD, and clinical studies examining the effect of pharmacological therapies on PSD are limited. Thus, there is a critical need to identify pharmacological treatments for PSD.

Swallowing is one of the most complicated tasks controlled by the central nervous system (CNS) as well as peripheral sensory and motor system.[5] Multiple brain regions including the brain stem, limbic system, cerebellum, and motor and sensory cortices play important roles in swallowing.[6] Enhancement of neuroplasticity using a pharmacological reagent that targets broad areas in the brain may present an important approach to improving central regulation of swallowing.

Several studies have demonstrated that a class of antidepressant, selective serotonin reuptake inhibitors, such as fluoxetine could improve structural and functional recovery from stroke by enhancing neuroplasticity and anti−inflammation-mediated neuroprotection, regulating cerebral blood flow, and modulating the autonomic nervous system.[7-9] Fluoxetine has been shown to increase hippocampal and cortical brain-derived neurotrophic factor (BDNF) mRNA expression, thereby improving neuronal survival and plasticity.[10-12] BDNF is an important component of neurotrophin growth factors and is widely distributed in the CNS and its periphery. It is mainly synthesized by neurons and plays an important role in plasticity and neurological function.[13] In addition, Snyder's study showed that fluoxetine facilitated the survival of newborn neurocytes via its antiapoptotic effect and improved the recovery of neurological function.[14] Moreover, in animal models, fluoxetine reduced microglia activity and neutrophil infiltration in the cerebral ischemic area, decreased the risk of cerebral infarction, and promoted motor recovery.[15] Administration of fluoxetine at an early stage of cerebral ischemia induced an anti-inflammatory effect on the CNS. Furthermore, it was reported that early application of fluoxetine promoted a positive neurological prognosis by developing an antioxidant stress effect.[16]

Treatment with fluoxetine was associated with reduction in disability level as measured by modified Rankin Scale scores at 1 year compared with placebo.[17] The beneficial effects of treatment continued for at least 1 year. A randomized, double-blind, placebo-controlled trial (FLAME trial−-Fluoxetine for motor recovery after acute ischemic stroke) reported that fluoxetine combined with physical therapy for 3 months' enhanced motor recovery in ischemic stroke patients with moderate to severe motor impairment.[18] Studies have shown that fluoxetine may improve patients' modified Rankin Scale scores,[17] National Institute of Health Stroke Scale (NIHSS) scores, and neurological functional outcomes.[19]. The findings of the FLAME trial[18] suggest that treatment during the first 3 months after stroke might be important to maximize recovery.

It has been proposed that PSD may be caused by damage to the cortex and subcortical structures, and swallowing recovery is led by cortical reorganization.[20] In the past few years, videofluoroscopy, transcranial magnetic stimulation, and magnetoencephalography were used to study swallowing activation after stroke. The findings suggest that reorganization and increased activity in the contralesional hemisphere play an important role in swallowing recovery.[21,22] Neuroplasticity may be integral in swallowing functional rehabilitation.[23]

Based on these studies, we hypothesized that fluoxetine could improve dysphagia by enhancing neuroplasticity. In this pilot study, we performed a clinical retrospective study to investigate the potential effects and mechanisms of fluoxetine on the recovery of PSD.

Materials and Methods

Study Population

This was a retrospective study. The study was approved by the Institutional Review Board of the participating hospital. Consecutive stroke patients admitted to an urban acute rehabilitation hospital from March 12, 2014 to July 7, 2015 were routinely evaluated for dysphagia upon admission. Their chief complaint was commonly reported in the evaluation by speech language pathologists as "difficulty swallowing," "unable to swallow pills," and "choking episode on pureed food." The patients' clinical data were obtained through electronic medical records. Inclusion criteria included the following: (1) ≥18 years old; (2) stroke confirmed by either computed tomography of the head or brain magnetic resonance imaging; and (3) admission and discharge swallowing scores following evaluation by speech language pathologists as standard routine treatment using the American speech-language-hearing association/functional communication measures (ASHA/FCM) Scale.[2] Exclusion criteria included the following: (1) presence of a prestroke swallowing disorder; (2) transfer to acute care hospital during rehabilitation; and (3) patient's length of stay was longer than the average day plus 2-fold standard deviation of each group.