A randomized, double-blind trial of bromocriptine efficacy in nonfluent aphasia after stroke

Abstract—The authors assessed the efficacy of bromocriptine in nonfluent aphasia after stroke in a 16-week, randomized, double-blind, placebo-controlled clinical trial conducted from June 2002 to April 2004. In all 38 patients after 4 months of treatment, improvement in both the bromocriptine and placebo treatment groups was observed ($p < 0.001$). The analysis of repeated-measures analysis of variance revealed bromocriptine did not improve nonfluent aphasia.

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Bromocriptine mesylate, an ergot derivative, is a sympatholytic dopamine D₂ receptor agonist that exerts inhibitory effects on serotonin turnover in the CNS. In partial lesions, such as those associated with nonfluent aphasia, postsynaptic dopaminergic agents, such as bromocriptine, could improve frontal lobe function. However, the effect of bromocriptine on nonfluent aphasia in stroke patients is not clear.^{1–9} Some trials showed no effect^{1,2,4} and others showed a positive effect,^{3,5–9} but these studies were mostly small open-label studies. Therefore, we conducted a large double-blind study to determine whether bromocriptine can be used in the clinical setting for the management of nonfluent aphasia after stroke.

Methods. Thirty-eight nonfluent aphasic stroke patients in an acute phase were recruited from the neurology emergency department of Isfahan University of Medical Sciences Hospitals, Isfahan, Iran, between June 2002 and April 2004. Entry criteria included age 80 years and younger, right-handedness, Persian speaking, and availability for follow-up for 4 months. All patients had no evidence of cardiac, hepatic, renal, or other chronic or neuropsychiatric disorder, as determined by history, physical examination, and screening laboratory tests. Neurologic examination, language assessment, routine blood tests, EKG, and brain CT or MRI were performed before study entry. The nature of the trial was explained to the patient or their first-degree relatives and his or her written consent obtained. Tenets of current version of the Declaration of Helsinki were followed, and institutional ethical committee approval was granted.

The 38 participants were assigned randomly and equally to one of the two treatment groups by flipping a coin at the time of study entry. The first treatment group received bromocriptine in a 2.5-mg/day increment over 4 weeks to 10 mg/day for a total of 4 months. The second group received a placebo. The placebo was identical in appearance and packaging to the active drug. The dose of bromocriptine or matching placebo remained constant during the following 16 weeks of the study. All patients tolerated the dose-escalation protocol without major side effects. Therefore, no participants were excluded from the study.

The trial was double blinded in that both patient and speech therapist were not aware of treatment type that the patient was

received. Patients were evaluated at 0, 8, and 16 weeks after the start of the therapy to evaluate possible side effects, compliance of the patients, and efficacy measurements. Language assessment was performed by a speech therapist and included a standardized Persian language test (composed of seven subsets to evaluate naming, verbal fluency, gesture to command, single-word responses, repetition, automatic speech, prosody, and global score).¹⁰ A global score of aphasia was calculated from a total score of 70. All measurements were repeated at 2 and 4 months after treatment with bromocriptine or placebo.

Statistical analysis. The study was powered (80%) to detect (with a two-sided α of 0.05) a mean difference in verbal fluency from a baseline of 2.6. Statistical analysis was based on an intention-to-treat principle. Comparison between groups receiving bromocriptine and placebo was made using independent Student's *t* test and analysis of variance (ANOVA) with repeated measures over time; comparisons between before and 4 months after treatment within each group were made by a paired Student *t* test.

Results. Thirty-eight patients (20 [52.6%] men, 18 [47.4%] women) who met the entry criteria were enrolled in the study. The patients who completed treatment were available for follow-up at 8 and 16 weeks. The two treatment groups were generally well matched at baseline with regard to age and gender. The mean (SD) age of bromocriptine group was 54.4 (11.4) and was 52.8 (14.4) years in placebo group.

Changes of verbal fluency, gesture to command, naming, single-word responses, repetition, automatic speech, prosody, and global score before and after receiving bromocriptine or placebo are shown in table 1. At 4 months, verbal fluency, gesture to command, naming, single-word responses repetition, automatic speech, prosody, and global score had significantly improved for both intervention and placebo groups. The overall repeated-measures ANOVA revealed improvement in both treatment groups ($p < 0.001$).

The overall analysis of repeated-measures ANOVA revealed no significant differences in the verbal fluency, gesture to command, naming, single-word responses, automatic speech, repetition, prosody, and global score at the end of trial between bromocriptine and placebo groups (table 2).

Discussion. In this study, both bromocriptine and placebo improved language (verbal fluency, gesture to command, naming, single-word responses, automatic speech, prosody, and global score) after 4 months of treatment in an acute phase in stroke patients. The bromocriptine and placebo groups were similar in their improvement from baseline to the end of the trial in average subtest and global scores.

Several open-label trials have tested the effects of bromocriptine on patients with nonfluent aphasia

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Table 1 Comparison of language tests in 38 stroke patients before and after treatment with bromocriptine and placebo

Test	Bromocriptine (n = 19)			Placebo (n = 19)		
	Mean (SD)		Differences (95% CI)	Mean (SD)		Differences (95% CI)
	Baseline	After therapy		Baseline	After therapy	
Verbal fluency	3.5 (1.7)	9.6 (0.7)	-6.1 (-7.1 to -5.2)***	3.5 (1.9)	9.1 (1.4)	-5.6 (-6.6 to -4.5)***
Gesture to command	5.0 (1.7)	12.6 (11.8)	-7.6 (-13.3 to -1.8)*	4.9 (1.6)	9.7 (1.1)	-4.8 (-5.6 to -4.1)***
Naming	5.3 (2.4)	9.9 (0.5)	-4.6 (-5.8 to -3.4)***	5.0 (2.1)	9.9 (0.5)	-4.9 (-6.0 to -3.8)***
Single-word responses	5.5 (1.8)	10.0 (0.1)	-4.5 (-5.5 to -3.6)***	6.1 (1.7)	10.0 (0.1)	-3.9 (-4.8 to -2.9)***
Automatic speech	3.3 (0.1)	10.0 (0.1)	-6.7 (-6.8 to -6.6)***	4.2 (1.7)	10.0 (0.1)	-5.8 (-8.5 to -3.1)**
Prosody	3.3 (0.1)	8.3 (2.4)	-5.0 (-6.1 to -3.9)***	3.3 (0.1)	6.7 (0.1)	-3.4 (-3.5 to -3.3)***
Repetition	4.2 (1.7)	9.2 (1.7)	-5 (-8.1 to -1.9)*	3.3 (0.1)	8.3 (2.4)	-5.0 (-6.1 to -3.9)***
Global score	17.7 (9.6)	64.0 (16.0)	-46.3 (-50.7 to -41.9)***	18.3 (9.6)	61.3 (16.3)	-43.0 (-48.3 to -37.6)***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

with variable results.¹⁻⁹ In a 62-year-old man with transcortical motor aphasia 3.5 years after his stroke, low doses (15 mg/day) of bromocriptine produced slight improvements in confrontation naming and the responsive naming and reductions in the number and proportion of pauses recorded in conversation.⁵ At the higher dose (30 mg/day), the improvements were less obvious. With the addition of two more patients, the effect of bromocriptine administration was similar.⁶ In another study¹ of two patients with nonfluent aphasia, a low dose of bromocriptine produced some improvement. In a study,² up to 60 mg/day of bromocriptine was used for 2 weeks and did not improved language. In a study of seven patients with moderate to severe nonfluent aphasia, the moderate severity group had significant improvement at doses of 30 to 60 mg/day.⁷ Additionally, performance on all measures generally declined when bromocriptine was decreased. Members of the severe group had no improvement in language production during the course of bromocriptine treatment. In four Turkish adults with nonfluent aphasia, bromocriptine was reported to have no effect on any of the subtest scores.⁴ In an open-label study, 20 mg/day bromocriptine produced improvements in verbal fluency measures and no significant improvement in gesture or

emotional prosody in a 50-year-old man with nonfluent aphasia.⁸ Finally, the effects of bromocriptine at a dose of 15 mg/day were studied in four patients with nonfluent aphasia, and improvement was found in word retrieval.⁹ In summary, these eight studies involved a total of 23 patients, varying in gender, age, site and size of the lesion, type of aphasia, and time post-onset of stroke, and thus firm conclusions regarding the effects of bromocriptine on nonfluent aphasia are difficult to make. In addition, some of the tools used to measure word finding and verbal fluency were subjective, while others were objective but arbitrarily defined. Statistical analyses did not always deal with the small number of patients and the small effect sizes. In addition, the improvement in verbal fluency across experimental phases might have been caused by spontaneous recovery independent of drug treatment. In a study of 25 nonfluent aphasic patients randomized to receive bromocriptine combined with speech therapy or placebo in an 18-week, double-blind study, improvement in dictation, reading comprehension, repetition, and verbal latency was observed.³ The improvement in repetition observed seem to be very small and improvement observed in dictation seems to be related to speech therapy per se.

Although this is a large placebo-controlled trial of a treatment of nonfluent aphasia in the acute phase of stroke, it is still limited by a relatively low power to find differences. The possible explanation for the discrepancies between these results and those of previous studies might be related to some methodologic differences, such as patient selection, the examination of patients at different stages in the natural history of stroke, and bromocriptine dose.

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Transient prosopagnosia after ischemic stroke

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An 89-year-old woman presented with acute left homonymous hemianopsia. T2-weighted cerebral MRI demonstrated an occipito-temporal ischemia (figure A). While hemianopsia eased within days, the patient noticed an inability to recognize her face in the mirror. A face recognition test proved complete prosopagnosia. This specific form of visual agnosia is considered typical for ventral occipito-temporal lesions involving the “fusiform face area.”¹ Lesion studies indicate that unilateral right but rarely left occipito-temporal lesions cause prosopagnosia.²

Months later, face recognition had gradually returned. Functional MRI with presentation of faces now revealed exclusive activation of the left fusiform gyrus (figure B), suggesting that reorganization may have occurred.

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Figure. (A) T2-weighted MRI with circumscribed ischemia of right fusiform gyrus (arrow). (B) Follow-up after recovery of face recognition: functional blood oxygenation level-dependent MRI demonstrates exclusive activation on contralateral side.

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