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Does long term use of piracetam improve speech disturbances due to ischemic cerebrovascular diseases?

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ABSTRACT

Aphasia causes significant disability and handicap among stroke survivors. Language therapy is recommended for aphasic patients, but not always available. Piracetam, an old drug with novel properties, has been shown to have mild beneficial effects on post-stroke aphasia. In the current study, we investigated the effects of 6 months treatment with piracetam on aphasia following stroke. Thirty patients with first-ever ischemic strokes and related aphasia were enrolled in the study. The scores for the National Institutes of Health Stroke Scale (NIHSS), Barthel Index (BI), modified Rankin Scale (mRS), and Gülhane Aphasia Test were recorded. The patients were scheduled randomly to receive either 4.8 g piracetam daily or placebo treatment for 6 months. At the end of 24 weeks, clinical assessments and aphasia tests were repeated. The level of improvement in the clinical parameters and aphasia scores was compared between the two groups. All patients had large lesions and severe aphasia. No significant difference was observed between the piracetam and placebo groups regarding the improvements in the NIHSS, BI and mRS scores at the end of the treatment. The improvements observed in spontaneous speech, reading fluency, auditory comprehension, reading comprehension, repetition, and naming were not significantly different in the piracetam and placebo groups, the difference reached significance only for auditory comprehension in favor of piracetam at the end of the treatment. Piracetam is well-tolerated in patients with post-stroke aphasia. Piracetam taken orally in a daily dose of 4.8 g for 6 months has no clear beneficial effect on post-stroke language disorders.

1. Introduction

Aphasia describes the impairment in linguistic subsystems, including semantics, phonology, or syntax, due to brain injury and most commonly stroke. In fact, 12–38% of stroke patients have aphasia (Greener, Enderby, & Whurr, 2001). Post-stroke aphasia causes devastating cognitive decline and morbidity in stroke survivors.

Recovery from aphasia is accompanied by peri-lesional activation in the left hemisphere or activation of homologous areas in the right hemisphere (Weiller, 1998). Intensive speech and language therapy is the only recommended treatment for aphasia (Bhogal, Teasell, & Speechley, 2003). However, speech and language therapy is not always feasible because of the high cost of the therapy and the small number of trained speech therapists in the developing countries, where stroke is more common.

Piracetam is a gamma-aminobutyric acid derivative with a potential effect on cognitive and amnestic functions (Winnicka, Tomasiak, & Bielawska, 2005). Experimental and clinical studies have suggested that piracetam has novel properties which may be beneficial for post-stroke aphasia (Greener et al., 2001). Piracetam facilitates or restores cholinergic, glutamatergic, and excitatory neurotransmission, and improves cerebral metabolism (Boissezon, Peran, Boysson, & Demonet, 2007; Kessler, Thiel, Karbe, & Heiss, 2000). When given in the acute phase of stroke, as an adjuvant to speech therapy, piracetam improves written language, naming on confrontation, and comprehension, as well as spontaneous speech, especially communicative verbal behavior, and the semantic and syntactic structure of speech (Huber, 1999; Kessler et al., 2000). The ability of cortical areas to learn from specific rehabilitative measures, such as speech therapy, might be enhanced by piracetam (Jordan & Hillis, 2006; Kessler et al., 2000). However, to date, the longest follow-up period of piracetam use in post-stroke aphasic patients is 3 months. The long-term benefits of the drug are still unknown. In the current study, we investigated the effects of piracetam on aphasia following stroke for 6 months.

2. Patients and methods

2.1. Participants

The current study was conducted in the Department of Neurology of Ondokuz Mayıs University Health Practice and Research Hospital between May 2005 and December 2009. One-hundred-three

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patients with acute onset aphasia and diagnosed with ischemic stroke according to the WHO criteria in the middle cerebral artery territory were enrolled for the primary evaluations of the study (WHO, 1989). The diagnosis of cerebral infarction was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). Electrocardiography (ECG) or 24-h ECG monitoring, transthoracic and transesophageal echocardiography with agitated saline, if required, duplex ultrasound of the carotid and vertebral artery, and brain and neck CT or MRI angiography were used to determine stroke subtype. Patients with a history of language or articulation disorders, stroke, dementia, progressive neurodegenerative diseases, severe auditory or visual disturbances, and post-stroke seizures before the baseline assessment were excluded. Also, patients with venous infarctions and intracerebral hemorrhage, including intra-infarct hemorrhage, who were likely to have better outcomes, or those who received thrombolytic treatment were excluded.

The patients or their relatives were informed about the study and gave written informed consent. The study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

2.2. Study design

This was a single-center, prospective, randomized, single-blind and placebo controlled study. Among 103 patients with aphasia subsequent to stroke, 42 patients did not meet the inclusion criteria, and seven refused to participate, five patients were excluded because of other reasons like inappropriate diagnosis and late clinical assessment. Twenty-six patients were randomized to placebo group according to age using a range of stratification for 3 years; of whom, four patients were lost to follow up during the course of the study, and seven patients died. Twenty-three patients were randomized to piracetam group; of whom, one patient deceased and seven patients were lost to follow up (Fig. 1). None of the deaths was attributed to the usage of the study drug. The randomization is generated by drawings.

Each patient underwent clinical assessment for post-stroke morbidity and aphasia at the beginning of the study and were scored quantitatively with modified Rankin Scale (mRS), Barthel Index (BI), National Institute of Health Stroke Scale (NIHSS) and Gülhane Aphasia Test (GAT). Thus, 6 month follow-up data were available for 30 patients. Fifteen patients received oral piracetam at a daily dose of 4.8 g, while 15 patients received placebo at the same dose.

At the end of 24 weeks, clinical assessments and aphasia tests were repeated while still on drug/placebo therapy, and a questionnaire addressing the possible side effects was applied to the patients.

The patients and their relatives were blinded to the study drug, but the investigators not. None of the patients received any other central nervous system stimulating or depressing drugs which may be effective on aphasia rather than the medications for secondary stroke prophylaxis, and language rehabilitation.

2.3. Clinical and aphasia assessment

Other factors which may have influence on recovery, like age, gender, smoking status and co-existing morbidities (hypertension [HT], diabetes mellitus [DM], coronary artery disease [CAD], hyperlipidemia [HL], atrial fibrillation [AF]) were recorded.

The severity of aphasia was evaluated quantitatively by the Gülhane Aphasia Test (GAT), which has been validated and widely used in Turkish-speaking populations (Mavis, Colay, Topbas, & Tanrıdag, 2007; Ozbudak, Altinok, Aydin, & Koseoglu, 2006; Yavuzer, Güzelküçük, Küçükkdeveci, Gök, & Ergin, 2001). Patients with unconsciousness, especially with larger infarcts, were not tested during the acute phase of the stroke; such patients were awaited for 2–32 days (mean 11.47 days) to achieve full consciousness and the ability to perform the GAT.

The GAT assesses the following language skills: spontaneous speech, reading fluency, auditory comprehension, reading comprehension, repetition, naming, and writing (Tanridag, 1995). Since the patients were unable to perform the writing task due to severe paralysis of the dominant hand, we did not apply the writing task. Spontaneous speech and reading fluency were rated on 10 degrees. Assessment of the auditory comprehension was based on 20 items (nine verbal commands, five true or false questions, and six multiple choice questions), while reading comprehension was assessed based on 15 items (nine written commands and six matching of

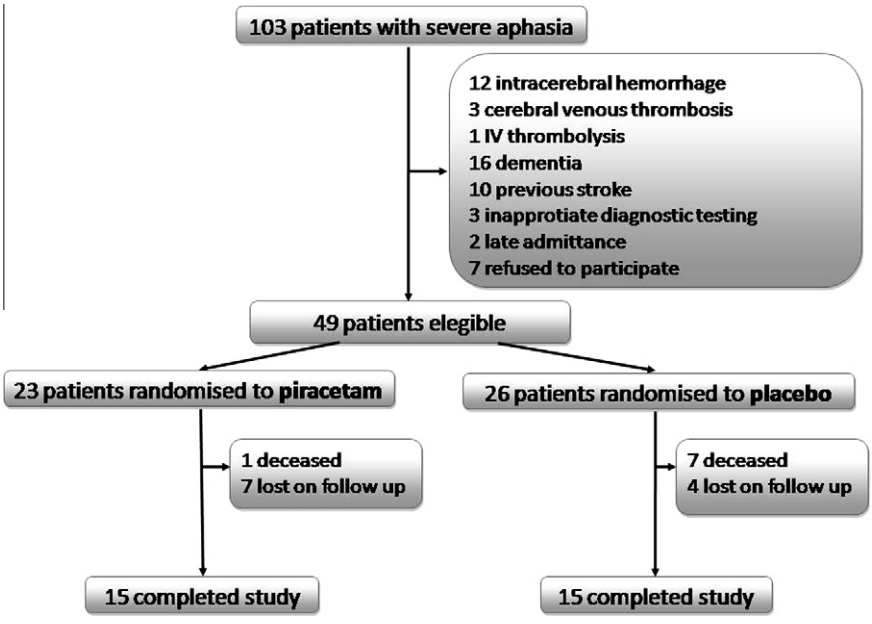

Fig. 1. The CONSORT diagram of the flow of participants.