The Effect of *Ginkgo biloba* on Functional Outcome of Patients with Acute Ischemic Stroke: A Double-blind, Placebo-controlled, Randomized Clinical Trial

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Background: Acute ischemic stroke is a major cerebrovascular disease with potential morbidity and mortality. Despite the availability of thrombolytic therapy in some centers, risk factor modification and rehabilitation therapy are the mainstays of stroke management. There is supporting evidence that *Ginkgo biloba* may afford neuroprotection and improve the outcomes of patients with acute ischemic stroke. *Methods:* In a double-blind, placebo-controlled, randomized controlled trial, we assessed the efficacy of *G biloba* on functional outcome in patients with acute stroke. The National Institutes of Heath Stroke Scale (NIHSS) was used to measure functional outcome. A total of 102 patients with acute ischemic stroke were studied. All patients received either *G biloba* or placebo tablets for 4 months. This trial was registered to the Iranian Registry of Clinical Trials (www.irct.ir; trial IRCT138804212150N1). *Results:* There were 52 patients who received G *biloba* and 50 patients who were in the placebo group. Age, sex distribution, previous medical condition, and laboratory data did not have any significant difference between the 2 groups ($P > .05$). The mean difference of 4-month follow-up NIHSS scores and NIHSS scores at admission was 4.7 ± 2.7 and 4.1 ± 3.0 in the *G biloba* and placebo groups, respectively ($P > .05$). The primary outcome—a 50% reduction in the 4-month follow-up NIHSS score compared to the baseline NIHSS score—was reached in 17 patients (58.6%) and 5 patients (18.5%) in the *G biloba* and placebo groups, respectively ($P < .05$). The risk ratio and number needed to treat were 3.16 (confidence interval 1.35-7.39) and 2.50 (confidence interval 1.58-5.90), respectively. In addition, multivariate regression adjusted for age and sex revealed a significant NIHSS decline in the *G biloba* group compared to the placebo group ($P < .05$). *Conclusions:* Our data suggest that *G biloba* may have protective effects in ischemic stroke. Therefore, the administration of *G biloba* is recommended after acute ischemic stroke. **Key Words:** Acute ischemic stroke—cerebrovascular—*Gingko biloba*—randomized controlled trial—thrombotic.

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Stroke is one of the leading causes of death in the world and the main cause of disability in adults.[1,2] Acute ischemic stroke (AIS) accounts for 88% of stroke events.[3] Despite the success of reperfusion therapies in patients with AIS, these therapies are only available to a minority of patients—and even patients who receive reperfusion therapy are at risk of neuronal death because of secondary neurodegenerative mechanisms.[4] Therefore, intensive care of the affected patients in the acute phase of stroke, risk factor modification, and rehabilitation remain the primary strategies in the management of AIS.[5-7] So far, no potentially neuroprotective drug has been introduced to improve outcomes after stroke.[5,8,9]

Current therapies are aimed to reduce the morbidity and mortality related to AIS.[10,11] In addition to acute thrombolytic therapy and risk factor modification strategies, a number of drugs have been used to improve neuronal function and protect neurons from ischemic degeneration.[12-14] During AIS, neuronal damage is caused by ischemia-induced hypoxia in brain tissue while subsequent hypoxic intracellular events lead to mitochondrial damage and cell death.[15] In addition, ischemia induces the production of oxygen-free radicals and other reactive oxygen species.[12] Agents affecting these neurodegenerative processes are believed to diminish neuronal damage and improve outcome in patients with AIS.

Gingko biloba, one the world's oldest living tree species, has been used as a traditional remedy for many years.[16] It was used by traditional Chinese physicians for variety of problems,[17] while many propose that *G biloba* might provide protection against neuronal injury in a number of neurodegenerative diseases.[18] The effects against ischemic stroke have not been evaluated comprehensively, but its neuroprotective mechanism needs to be completely studied.[19] It has been hypothesized that *G biloba* extracts might protect neuronal cells against oxidative stress, providing potential neuroprotective effects during ischemic cerebrovascular events.[20]

Despite the possible neuroprotective effects of *G biloba*, there is not enough evidence to recommend its use in the management of ischemic stroke.[21] In addition, there is no convincing evidence supporting the routine use of *G biloba* to promote recovery after ischemic stroke.[22] Therefore, sought to reveal whether patients with AIS benefit from *G biloba* extract administration and to assess the effect of *G biloba* on the functional outcomes of patients with AIS.

Methods

Study Outline

In a prospective, randomized, placebo-controlled clinical trial, we studied 102 consecutive patients with AIS who were admitted to Tabriz Imam Reza and Razi Hospitals, 2 tertiary level hospitals in East Azerbaijan province, Iran, between January 2009 and September 2011. The inclusion criteria included being 45 years of age or older and having the involvement of anterior cerebral circulation. The exclusion criteria were having the indication of anticoagulant therapy, patients with chronic kidney, hepatic, and hematologic diseases, pregnant or lactating women, and profound loss of consciousness (i.e., stupor and coma). The reason for selection of patients with involvement of anterior circulation was that in our centers, patients with posterior circulation insufficiency receive anticoagulation agents that cannot be used simultaneously with *G biloba*.

Case and Control Groups

Patients were randomly divided into 2 groups: the case group, comprised of 52 patients who received *G biloba* tablets (Gol-Darou Company, Isfahan, Iran) with a total dose of 120 mg/day (40 mg 3 times/day),[23] and the control group, comprised of 50 patients who received placebo tablets that were similar to the *G biloba* tablets in size, shape, and color (Fig 1). The treatment course lasted for 4 months. Randomization of patients was performed by an allocation sequence, generated with computer random number generator (Randlist version 11 software package; DatInf GmbH, Tübingen, Germany). Allocation was concealed by the use of sequentially numbered opaque envelopes. Written informed consent was obtained from all the patients before their allocation to the study. The protocol of this study was approved by the ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran and registered in the Iranian Registry of Clinical Trials (www.irct.ir; trial IRCT138804212150N1).

All patients were visited every month for 4 months and asked to bring the remaining drugs (*G biloba* or placebo) to check whether they had taken the medications completely. The patients were assessed for hemorrhagic complications and recurrent stroke at follow-up visits.

Study Variables

The National Institutes of Health Stroke Scale (NIHSS) score, measured from 0 to 42, was used by neurology residents and attending physicians to assess the clinical severity and functional ability of ischemic stroke patients quantitatively on admission and discharge days, and throughout 4-month follow-up sessions.[24]

Demographic variables consisted of age, sex, smoking, history of previous stroke or transient ischemic attack, oral contraceptive pill use, hypertension, diabetes, hyperlipidemia, coronary artery disease, dysrhythmias, and intracranial hemorrhage. The biochemical and hematologic