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ORIGINAL ARTICLE

Intravenous administration of EGB 761 and 90-day functional outcome in patients with acute ischemic stroke

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Abstract

Background & Objective: EGB 761 is a standardized natural extract used to treat impaired cerebral perfusion and nutrition (cerebrovascular insufficiency) in Korea. Although several animal studies have been conducted, few studies have investigated the clinical effects of EGB 761 in acute stroke. This study assessed the clinical benefit of intravenous EGB 761 in patients with acute ischemic stroke. *Methods:* This retrospective study examined a prospectively collected stroke database. We evaluated 232 patients with acute ischemic stroke within 48 hours of symptom onset. All patients were treated with antiplatelet or anticoagulation agents. We compared baseline characteristics between the EGB 761-treated and non-treated groups. The functional outcome measure was the modified Rankin Scale (mRS) score 90 days after stroke onset. *Results:* Of the 232 patients, 170 received EGB 761 during the first 3 days after arrival in the emergency department. We found no significant differences in baseline characteristics between the groups, with the exception of atrial fibrillation (p=0.032). After adjusting for baseline factors, intravenous administration of EGB 761 was associated with an improved 90-day functional outcome (mRS ≤2) compared with the control group (odds ratio, 2.56; p<0.05).
Conclusions: Our results showed a clinical benefit of intravenous EGB 761 in patients with acute ischemic stroke.

INTRODUCTION

Ischemic stroke is a leading cause of disability in the United States and worldwide.[1] Ischemic strokes, which comprise approximately 80% of all strokes, are characterized by complex spatial and temporal events that evolve over hours or even days.[2] Intravenous recombinant tissue plasminogen activator (rt-PA) is the only proven treatment for acute ischemic stroke, if started within 3–4.5 hours of symptom onset.[3] Approximately one-fourth of patients with ischemic stroke arrive within the time window for rt-PA therapy, and this percentage has not changed in recent years.[4] A large percentage of patients are ineligible for hyperacute therapy based on the time criterion alone. Therefore, more treatment options are needed for patients with acute ischemic stroke.

Ginkgo biloba/EGB 761® (EGB 761) is a popular, standardized natural extract used to treat impaired cerebral perfusion and nutrition (cerebrovascular insufficiency) in Korea. EGB 761 is a mixture of substances with a wide variety of physical and chemical properties and activities. Numerous pharmacological investigations have led to the conclusion that the terpene trilactones and flavonoids in EGB 761 are responsible for the main pharmacological effects of the extract.[5] The pharmacological mechanisms of EGB 761 include modification of Ca^{2+} signaling, clearing oxygen free radicals, decreasing lipid peroxidation, and promoting synthesis and release of epoprostenol.[6]

Although several animal studies have been conducted[6-9], few have investigated the clinical effect of EGB 761 in patients with acute ischemic

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stroke. This study assessed the clinical benefit of intravenous administration of EGB 761 in patients with acute ischemic stroke.

METHODS

Patient selection, data acquisition, and outcome measure

This was a retrospective study on a prospectively collected stroke database. We evaluated 232 patients with acute ischemic stroke who presented to the emergency room within 48 hours of symptom onset between August 2011 and October 2012. All patients underwent a neurological examination, routine blood testing, electrocardiogram, magnetic resonance imaging, and magnetic resonance angiography. All patients were treated with an antiplatelet or anticoagulation agent according to their stroke subtype.

Inclusion criteria for this study were: adult men or women who were at least 18 years old; admission to the emergency department (ED) within 48 hours of symptom onset; and treatment with a total daily dose of 10 mL (35 mg) EGB 761 (Tanamin®; YuYu Pharma, Korea) initiated within 48 hours of stroke onset (EGB-treated group). EGB 761 was administered twice daily (half dose) during the first 3 days after arrival in the ED.

We compared baseline characteristics between the EGB 761-treated and untreated groups. The baseline clinical variables included age, sex, history of hypertension, diabetes mellitus, myocardial infarction, atrial fibrillation, glucose level, hematocrit level, platelet count, total cholesterol level, LDL cholesterol level, initial National Institutes of Health Stroke Scale (NIHSS) score, last normal time to ED arrival time, first abnormal time to ED arrival time, and whether patients were treated with rt-PA.

The functional outcome measure was the modified Rankin Scale (mRS) score at 90 days after stroke onset. We used symptomatic intracranial hemorrhage defined as a CT or MRI-documented hemorrhage that was temporally related to deterioration in the patient's clinical condition, if occurred, during the first 3 months as the safety outcome measure.

Statistical Analyses

Comparisons of quantitative variables between groups were performed with the Mann–Whitney *U*-test. Frequencies of categorical variables were compared between groups using the chi-square or Fisher's exact tests. Data are presented as means ± standard deviations. We assessed the relationship between the EGB 761-treated and untreated groups at the 90-day functional outcome using logistic regression analysis. *P*-values < 0.05 were considered significant. Analyses were performed using IBM SPSS 20.0 statistical software (IBM, Armonk, NY, USA).

Ethics statement

The study design was approved by the institutional review board at Chungbuk National University Hospital (IRB No. CBNUH 2013-08-002-002). The board waived the need to obtain informed consent.

RESULTS

In total, 232 patients were admitted to our stroke center with acute ischemic stroke within 48 h of symptom onset between August 2011 and October 2012. Among them, 170 (73.3%) received EGB 761 during the first 3 days of arriving at the ED, and 62 (26.7%) patients did not receive the extract.

The mean age of all patients was 67.35 ± 12.66 yr (EGB-treated group: 67.26 ± 12.29 yr, EGB-untreated group 67.60 ± 13.72 yr); 138 (59.5%) patients were men (EGB-treated group: 97 [57.1%], EGB-untreated group 41 [66.1%]). Patient baseline demographics and clinical characteristics are summarized in Table 1.

No significant difference was found in the baseline characteristics between the groups, with the exception of atrial fibrillation (EGB 761 group: 8.2% *vs.* control group: 19.4%; p=0.032).

Functional outcomes at 90 days are shown in Figure 1. EGB761-treated patients had no increase in the risk of symptomatic intracerebral hemorrhage compared with EGB-untreated patients (2/170 (1.2%) *vs*. 1/62 (1.6%); p=1.000). The percentage of patients with a good functional outcome at 90 days (mRS ≤ 2) was higher in the EGB-treated group than in the EGB-untreated group (139/170 (81.8%) *vs*. 39/62 (62.9%); p=0.003). After adjusting for confounding variables (age, atrial fibrillation, and initial NIHSS score), intravenous administration of EGB 761 was associated with a good 90-day functional outcome (mRS ≤ 2) compared with that in the control group in a multivariate analysis (odds ratio, 2.56; 95% confidence interval, 1.20–5.56; p=0.014) (Table 2). In addition, intravenous EGB 761 was also associated with a favorable 90-day functional outcome (mRS ≤1) (odds ratio, 2.04;

Table 1: Baseline characteristics of the study patients

	EGB 761 group (N=170)	Control group (N=62)	Total (N=232)	p-value[a]
Age, year (mean ± S.D.)	67.26±12.29	67.60±13.72	67.35±12.66	0.860
LNT to ER arrival time (hours)	16.65±18.32	17.13±16.71	16.78±17.87	0.857
FAT to ER arrival time (hours)	14.97±18.19	15.88±17.15	15.21±17.89	0.731
Initial NIHSS	3.17±3.74	4.27±4.68	3.46±4.02	0.105
Hematocrit (%)	39.10±6.74	40.13±10.62	39.38±7.95	0.385
Platelet count ($x10^3/\mu\ell$)	234.60±222.18	198.97±58.05	223.08±193.01	0.214
Total cholesterol ($mg/d\ell$)	153.82±47.03	159.47±39.53	155.29±45.18	0.410
Low density lipoprotein ($mg/d\ell$)	107.53±52.21	99.75±35.22	105.51±48.42	0.289
Glucose ($mg/d\ell$)	129.58±68.50	148.42±77.38	134.61±71.30	0.075
SBP (mmHg)	146.84±26.34	142.11±25.90	145.59±26.26	0.229
DBP (mmHg)	87.66±13.20	87.03±13.45	87.49±13.24	0.752
Gender				0.274
Male	97 (57.1%)	41 (66.1%)	138 (59.5%)	
Female	73 (42.9%)	21 (33.9%)	94 (40.5%)	
tPA treatment	6 (3.5%)	2 (3.2%)	8 (3.4%)	1.000
Hypertension	107 (62.9%)	37 (59.7%)	144 (62.1%)	0.764
Diabete mellitus	39 (22.9%)	20 (32.3%)	59 (25.4%)	0.203
Myocardial infarction	17 (10.0%)	4 (6.5%)	21 (9.1%)	0.565
Atrial fibrillation	14 (8.2%)	12 (19.4%)	26 (11.2%)	**0.032**

a: χ^2-test or student's t-test
LNT, last normal time
ER, emergency room
FAT, first abnormal time
NIHSS, National Institutes of Health Stroke Scale
SBP, systolic blood pressure
DBP, diastolic blood pressure
tPA, tissue plasminogen activator

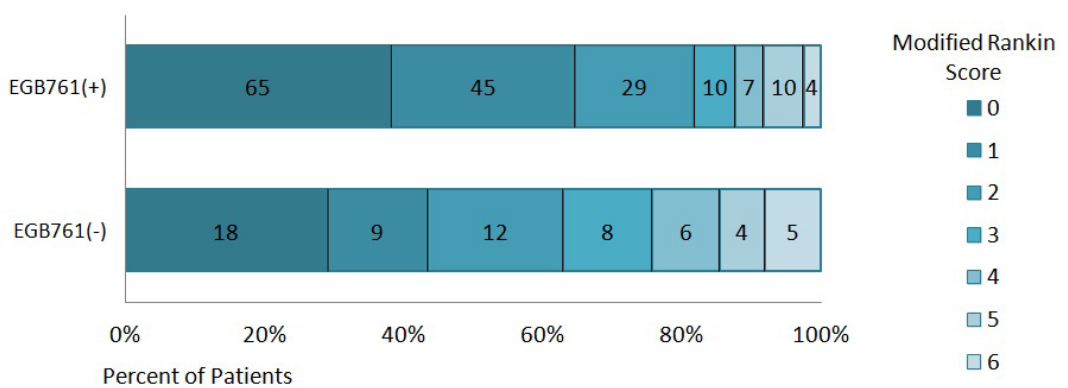

Figure 1. 90-day functional outcome according to the intravenous administration of EGB 761.

Table 2: Odds ratios and 95% confidence intervals (CIs) for good 90-day functional outcome according to multiple variations in the study population*

Variables	Odds ratio (95% CI)	p-value
Age (year)	0.93 (0.91– 0.97)	**<0.001**
NIHSS	0.85 (0.79–0.93)	**<0.001**
Atrial fibrillation (+)	0.94 (0.34–2.57)	0.901
EGB 761 (+)	**2.56 (1.20–5.56)**	**0.014**

NIHSS, National Institutes of Health Stroke Scale
*90 days mRS ≤2; good, mRS>2; poor

95% confidence interval, 1.01–4.13; p=0.047) (Table 3).

DISCUSSION

Our results show that intravenous administration of EGB 761 to patients with acute ischemic stroke had a clinical benefit at 90 days, with no increase in the rate of symptomatic intracranial hemorrhage during the first 3 months. In general, EGB 761 treatment had no serious adverse effects.[10,11]

EGB 761 reduces neuronal death in cases of focal and global brain ischemia.[12-14] However, previous studies have shown that EGB 761 improved acute stroke outcome only in animal models of rats or mice. Very few studies have investigated the clinical effect of EGB 761 in patients with acute ischemic stroke. Therefore, the clinical efficacy of such a standardized *Ginkgo biloba* extract in patients with stroke remains controversial.

EGB 761 has neuroprotective and antioxidant properties against various cardiovascular and neurological disorders, such as ischemia, Alzheimer's disease, and depression.[15-17] It also inhibits platelet aggregation and induces vasodilation as a platelet-activating-factor antagonist.[18] Our findings indicate that these potential effects of intravenous EGB 761 aid in the clinical recovery of patients with acute ischemic stroke.

Our data suggest that intravenous administration of EGB 761 to patients with acute ischemic stroke is feasible, safe, and potentially efficacious. Early recanalization of an occluded artery using rt-PA or a mechanical device is the only proven treatment for acute ischemic stroke, if started within 4.5–8 hours of symptom onset. However, this thrombolytic strategy is generally available only to a small number of suitable patients at a limited number of hospitals. The guidelines recommend initiating antiplatelet or anticoagulation therapy according to stroke subtype as soon as possible.[19,20] However, antiplatelet or anticoagulation therapy is effective only in preventing secondary stroke. Therefore, intravenous administration of EGB 761 may be a feasible additional treatment to improve clinical outcomes for patients during the acute ischemic stroke period.

Several limitations to this study should be mentioned. First, this study was a retrospective analysis of patients treated with or without intravenous EGB. The two groups were not

Table 3: Odds ratios and 95% confidence intervals (CIs) for favorable 90-day functional outcome according to multiple variations in the study population

Variables	Odds ratio (95% CI)	p-value
Age (year)	0.96 (0.93– 0.98)	**0.003**
NIHSS	0.74 (0.66–0.84)	**<0.001**
Atrial fibrillation (+)	0.65 (0.24–1.72)	0.383
EGB 761 (+)	**2.04 (1.01–4.13)**	**0.047**

NIHSS, National Institutes of Health Stroke Scale
*90 days mRS ≤1; favorable, mRS>1; unfavorable

randomly assigned. Thus, there was potential for bias during patient selection. The use of prospectively collected data contributed to minimize this problem. Second, this study had a small sample size, which limited the statistical power, and it was performed at a single center.

In conclusion, our results show a clinical benefit for intravenous administration of EGB 761 in patients with acute ischemic stroke, suggesting that infusion of the natural extract is a potential neuroprotective strategy for suitable patients. A large multicenter randomized controlled trial is needed to confirm this benefit.

DISCLOSURE

This work was supported by a research grant from Yuyu pharmaceutical.

Conflict of interest: None

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