Piracetam Prevents Cognitive Decline in Coronary Artery Bypass: A Randomized Trial Versus Placebo

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Background. Coronary artery bypass grafting (CABG) can be associated with postoperative cognitive impairment and ischemic stroke. No effective treatment is currently available. The aim of this study was to evaluate the effectiveness of piracetam to treat the cognitive impairment after CABG in an investigator-initiated, double-blind, placebo-controlled, randomized clinical trial.

Methods. Patients undergoing CABG (n = 98) were randomized to placebo (n= 48) or piracetam (n= 50). Study drugs were administered intravenously (150 mg/kg daily; 300 mg/kg on the day of surgery) from the day before surgery to 6 days after surgery, then orally (12 g/day) up to 6 weeks after surgery. Cognitive function was assessed before surgery (baseline) and 6 weeks after surgery (outcome) by using a battery of 12 neuropsychologic tests. The Spielberger Anxiety Inventory and the Beck Depression Inventory were also administered. The combined score derived from the standardized neuropsychologic assessments was analyzed by using an analysis of covariance with baseline and education as covariates.

Results. Six weeks after surgery, the combined score indicated a statistically significant treatment effect in the per protocol population (1.848, $p = 0.041$) and a tendency towards statistical significance in the intent-to-treat population (1.624, $p = 0.064$) in the group treated with piracetam, but no statistically significant treatment effect was seen in the placebo. The state of anxiety measured by the Spielberger Anxiety Inventory was decreased in both groups (−9.27 and −6.37 in the placebo and piracetam groups, respectively).

Conclusions. Six weeks after CABG, cognition was significantly improved in patients treated with piracetam. Additional trials are required to confirm these effects.

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Coronary artery bypass grafting (CABG) surgery is a common cardiac intervention recognized to be highly effective in stabilizing ventricular dysfunction [1]. The morbidity after CABG has decreased considerably during the past two decades because of improved surgical and patient management techniques. Nevertheless, a significant proportion of patients undergoing CABG are reported to develop postoperative cognitive impairments [1–4], ranging from slight to more pronounced disturbances and lasting some weeks, months, or years [1,2,5,6]. These cognitive impairments result in increased in-hospital mortality, longer duration of hospitalization, and increased use of resources [7].

The pathophysiologic mechanisms for postoperative cognitive decline associated with CABG are unknown but are probably multifactorial [1,2,6]. Microemboli [8,9], ischemic hypoperfusive brain lesions[10], low body temperature during surgery [11], individual susceptibility to cerebrovascular disease [12], and possession of the gene for apolipoprotein E ϵ4 isoform [13] are reported to be involved in this cognitive decline. A long-term cognitive decline has been reported 5 years after CABG surgery in 42% of patients [14], and similar neuropsychologic deficits have also been reported in patients 1 and 3 years after CABG and in comparable nonsurgical controls [3,4,15].

Despite several recent attempts, as yet no gold standard treatment has been devised for the cognitive impairments associated with CABG. Positive effects of prostacyclin [16], GM_1 gangliosides [17], remacemide [18], pexelizumab [19] and S(+)-ketamine [20] were either absent or questionable, although heparin [21], lidocaine [22], and piracetam [23] have been shown to be beneficial. The cognitive-enhancing properties of piracetam have been demonstrated in numerous studies [23,24]. Whereas in most other ischemic pathologies the drug is administered after the ischemia, the planning of CABG surgery allows administration of the drug before the ischemia. A more robust preventive effect should therefore be expected.

This was a double-blind, placebo-controlled clinical trial designed to assess the cognitive impairment after CABG and to evaluate the efficacy of piracetam in preventing this cognitive impairment. We hypothesized that a cognitive impairment would be obvious in placebo patients 6 weeks after surgery, and that piracetam would limit its extent.

Patients and Methods

Study Design

This investigator-initiated, exploratory phase IV, double-blind, placebo-controlled trial was conducted in accor-

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Table 1. Number of Patients and Demographic Characteristics Before Surgery

	Placebo	Piracetam
Number of patients (M/F)		
ITT Population	55 (43/12)	54 (47/7)
PP Population	48 (38/10)	50 (45/5)
Discontinued from the study	6 (10.9%)	5 (9.3%)
Level of education[a]		
Elementary	12 (22.4%)	3 (5.8%)
Secondary	36 (67.9%)	40 (76.9%)
Higher	5 (9.4%)	9 (17.3%)
Age (years)[b]	56.16 ± 5.51 (44–65)	55.50 ± 5.58 (43–65)
Body mass index (kg/m^2)[b]	27.65 ± 3.63 (20.8–36.0)	29.13 ± 3.59 (20.1–38.6)

[a] Two subjects in each treatment group had no data on education. Treatment groups are compared by Fisher's exact ($p = 0.032$) test for the level of education. [b] Data for age and body mass index are mean ± SD with ranges in parenthesis.

ITT = intention to treat; PP = perprotocol.

dance with the ICH Guideline for Good Clinical Practice [25] and local laws and regulations. After approval was obtained from the Debrecen University Institutional Ethics Committee on October 30, 2000, patients (1) about to undergo CABG surgery, (2) considered as mentally capable of adhering to the protocol, (3) with a sufficient level of education, (4) a Mini Mental State Examination (MMSE) score exceeding 20; and (5) who gave their written informed consent were screened from January 31, 2001, to June 10, 2004.

Patients were excluded for any of the following reasons: (1) radiologic signs of cerebral territorial infarcts, (2) ischemic attack within the previous month, (3) primary central nervous system degenerative diseases, (4) major psychiatric disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria, (5) brain tumor, (6) history of infectious or inflammatory brain disease, (7) cranial trauma within the 12 previous months, (8) previous or current cardiac valvular disease, (9) uncontrolled hypertension, (10) active gastric or duodenal ulcer or severe hepatic or renal insufficiency, or any disorder that could result in cognitive deterioration, (11) diagnosed malignancies or autoimmune disease, or (12) current use of any psychotropic drug or any other drug that could significantly affect cognitive function.

Patient Management and Treatments

Before surgery, patients had carotid Doppler and cranial computed tomography (CT) scans, routine laboratory tests (hematology, biochemistry, and urinalysis), baseline cognitive assessment through a battery of 12 neuropsychologic tests, and review of the inclusion and exclusion criteria. Eligible patients were randomly assigned to receive either placebo or piracetam. Both treatments were identical in shape, size, and color.

The study was conducted in two successive phases. In the first study phase, patients were hospitalized from the day before surgery and received intravenous (IV) placebo or piracetam 150 mg/kg divided into three equivalent doses (maximum, 12 g). On the day of surgery, patients received IV placebo or piracetam at 75 mg/kg before and during surgery and 150 mg/kg divided in two equivalent doses after surgery (maximum, 24 g). During the first 6 days after surgery, patients received IV placebo or piracetam (150 mg/kg daily) divided into three equivalent daily doses (maximum, 12 g daily).

In the second study phase, patients were discharged from the hospital 7 days after surgery and took oral placebo or piracetam (12 g daily) divided into 3 equivalent daily doses for 6 ±1 weeks. At the end of this period, patients returned to the hospital and were evaluated with carotid Doppler and cranial CT scans, the same routine laboratory tests as before surgery, and an end point cognitive assessment.

Neuropsychologic Assessments

Neuropsychologic evaluations were administered before surgery (baseline) and 6 ± 1 weeks after surgery (end point). These consisted of The Word Fluency test adapted to the Hungarian language [26], the Digit Symbol, the Digit Span, and the Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS) [27], the Trail Making test (Hungarian version of the "Nurnberger Alters-Inventar") [28], the Hungarian version of the Rey Auditory Verbal Learning test [29] (first recognition and delayed recall 30 minutes later), and the Pieron test [30]. The Simple Reaction Time, the Choice Reaction Time, and the Serial Reaction Time were used as described by Palombo and colleagues [31]. For the Word Fluency test, the Digit Symbol, Block Design, and Digit Span subtests of the WAIS, the Rey Auditory Verbal Learning test and the Pieron test, higher scores indicate better cognitive function. For the Trail Making test and for the three reaction time tasks, lower scores indicate better cognitive function.

The Spielberger State-Trait Inventory [32] provides a measure of both the state anxiety, and the trait or generalized anxiety. The Beck Depression Inventory [33] evaluates the depression. For both these inventories, higher scores indicate a greater anxiety or depression, respectively.