Journal of the Neurological Sciences 349 (2015) 117–123

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

An explorative study regarding the effect of L-deprenyl on cognitive and functional recovery in patients after stroke

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ARTICLE INFO

Article history:
Received 16 September 2014
Received in revised form 2 December 2014
Accepted 28 December 2014
Available online 3 January 2015

Keywords:
Stroke
Selegiline
L-Deprenyl
Pharmacological agents
Cognitive recovery
Rehabilitation

ABSTRACT

Introduction: Selegiline (L-deprenyl) is a selective monoamine oxidase type B inhibitor that has been shown to have neurotrophic and anti-apoptotic properties and to protect neurons in different experimental models of cerebral ischaemia. The aim of this explorative study was to investigate whether selegiline could enhance cognitive and functional recovery in stroke survivors.
Methods: This was a randomized controlled study in which patients enrolled within two weeks of stroke underwent a clinical and functional evaluation and a neuropsychological assessment. The patients were given selegiline (10 mg/day) or matched placebo once a day for six weeks in addition to standard rehabilitation care.
Results: Of 137 stroke survivors, 47 patients met the inclusion criteria and were randomly assigned to the Study Group (n = 23) or the Control Group (n = 24). The statistical analysis showed a significant improvement in most neuropsychological tests after two and six weeks in the study group; these improvements were not replicated in the control group. The between-group analysis revealed that the domains of attention and executive functions benefited most from the drug treatment. With regard to functional status, comparison of clinical scores at admission and discharge showed a statistically significant enhancement in both groups without statistically significant differences between the groups.
Conclusions: These preliminary results suggest that selegiline administered in the subacute phase can promote cognitive functioning in stroke patients. Further studies will elucidate whether and how this enhancement can impact on functional recovery in the short and in the long term.

1. Introduction

Stroke is one of the most devastating neurological conditions, associated with a detrimental impact on patients' health-related quality of life and high economic costs; worldwide it accounts for more than five million deaths annually, and 44 million disability-adjusted life-years lost [1–4].

Despite extensive research, no effective treatments are currently available to prevent or reduce stroke-related neuronal damage, or to promote recovery after stroke, and only physical therapy seems to support spontaneous functional recovery after the acute event [5].

Clinical trials of pharmacological agents in stroke have focused mainly on therapeutic steps that need to be taken in the very acute stage, for example to restore blood flow (thrombolytic therapy) or reduce the effects of ischaemia (neuroprotective therapy) [6,7]. However, thrombolytic therapy is effective only if it is administered within the first few hours of stroke onset and, so far, no neuroprotective therapy has proven to be efficacious in humans. There is thus a considerable need for new pharmacological strategies to improve outcome after stroke [8].

Selegiline (L-deprenyl) is a drug that has demonstrated antioxidant and neuroprotective effects, as documented in the permanent middle cerebral artery occlusion model in rats [9]. Widely used in the treatment of Parkinson's disease [10], selegiline is an irreversible inhibitor with selectivity for monoamine oxidase type B (MAO-B) that in recent studies showed anti-inflammatory and anti-apoptotic properties [11]. It has been shown to reduce total brain damage after transient hypoxia–ischaemia, to maintain mitochondrial membrane potential, and to eliminate oxygen radicals [12]. Moreover, it has been suggested that selegiline can prevent striatal neuronal necrosis [13], enhance the survival of hippocampal pyramidal cells [14], increase the secretion of neurotrophic factors [15], and improve learning and memory in rats [16]. Studies in humans demonstrated that selegiline is also an effective antidepressant whether administered orally or in a transdermal formulation [17]. In children with attention-deficit/hyperactivity disorder

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http://dx.doi.org/10.1016/j.jns.2014.12.039
0022-510X/

selegiline has been shown to reduce symptoms without producing undesirable side effects [18], while in the elderly it has been shown to exert a positive effect on cognition and functional abilities in patients with Alzheimer's disease [19]. Long-term use of selegiline has been reported to produce significant improvements in several cognitive domains in patients with HIV-associated cognitive impairment [20].

Taken together, these findings suggest that selegiline could possibly be a drug able to support cognitive and functional recovery after cerebrovascular damage. To date only one study [21] has investigated the effects of selegiline in promoting recovery after a recent ischaemic stroke. The authors administered selegiline within 48 h of the acute event at a dosage of 5 mg daily for the first three days and then 10 mg daily for three months. The following scales were considered as outcome measures: Scandinavian Stroke Scale (SSS), Barthel Index, Fugl-Meyer scale, the 15-Dimensional Measure of Health-Related Quality of Life test and the Zung Self-Rating Depression Scale. A clear trend in favour of selegiline for all the efficacy variables was found, although a statistically significant result was obtained only for the SSS. Despite these encouraging results, in our view this study suffered from some limitations, in particular its lack of measures to assess patients' cognitive status. For this reason, assuming that selegiline could, as its main effect, target cognitive functioning and that functional recovery, particularly the relearning of motor functions, may be mediated by cognitive retrieval, the aim of this study was to investigate the effectiveness of selegiline on cognition and functional recovery in stroke survivors.

2. Materials and methods

2.1. Participants

The study enrolled consecutive patients referred to our Neurorehabilitation Unit between 1st September 2011 and 31st August 2013. Inclusion criteria were: first-ever ischaemic or haemorrhagic (not evacuated) stroke confirmed by neuroimaging (computed tomography, CT or magnetic resonance, MR); acute event within the previous two weeks; Mini-Mental State Examination (MMSE) [22] score of between 10 and 23; Functional Independence Measure (FIM) [23] score ≤ 60. Exclusion criteria were: progressing stroke; brain tumours; subdural haematoma; multiple sclerosis; multi-infarct dementia; epilepsy; psychiatric diseases; severe cardiovascular disease [especially: severe or unstable angina pectoris, moderate to severe heart failure (NYHA III)]; myocardial infarction within the last six months; severe or treatment-resistant hypertension (WHO III) diagnosed before the stroke; severe or treatment-resistant cardiac arrhythmias diagnosed before the stroke; severe renal or hepatic dysfunction; congenital metabolic diseases; active duodenal or gastric ulcer; severe anaemia (Hb < 100 g/L); neglect and speech disturbances (aphasia); premorbid IQ score < 70 or pre-existing dementia; Hamilton Depression Rating Scale (HDRS) [24] score > 7; abuse of drugs or alcohol; hypersensitivity to selegiline or agents chemically related to it; the use of α2-adrenergic receptor agonists (e.g., clonidine), α1-adrenergic receptor antagonists (prazosin), cholinergic or anticholinergic drugs, nimodipine, fluoxetine, antidepressants, or other drugs affecting the central nervous system [e.g., y-aminobutyric acid (GABA)ergic drugs such as benzodiazepines].

All patients gave their written informed consent to take part into the study. The study was approved by the local ethics committee and was conducted in accordance with the revised version of the Helsinki Declaration.

2.2. Measures

All the patients underwent a complete clinical and neurological examination, including cognitive and functional evaluations.

The neuropsychological evaluation assessed different cognitive domains: global cognitive functioning (MMSE, Montreal Cognitive Assessment — MoCA) [22,25], working memory (Digit Span and Corsi's Test) [26], episodic memory, immediate and delayed recall (Rey Auditory Verbal Learning Test — RAVLT) [27], logical memory, immediate and delayed recall [28], non-verbal reasoning (Raven's Coloured Progressive Matrices 47 — PM47) [29], frontal functionality (Frontal Assessment Battery — FAB) [30], simple speed processing and complex attention (Trail Making Test A — TMTA and Trail Making Test B — TMTB, respectively) [31], visual selective attention (Attentive Matrices) [32], directed attention and inhibitory control (Stroop test: time-StroopT and errors-StroopE) ([33]), visuo-motor coordination (Symbol Digit Modalities Test — SDMT) [34], verbal fluency, both phonological and semantic [35], visuo-constructional abilities (Rey-Osterrieth Complex Figure, copy) ([36]), language (Aachener Aphasie Test — AAT) [37]. All neuropsychological measures were validated and Italian population-based norms were available for all tests.

Clinical status was evaluated by means of the National Institutes of Health Stroke Scale (NIHSS) [38], while the functional status was assessed with the FIM.

All the evaluations were performed by the same neurologist and neuropsychologist, external to the clinical management and blinded to the group assignment of the patients.

2.3. Study design

The patients who met the inclusion criteria were randomized, by means of a computer-based random-number generator, to receive either selegiline (Study Group, SG) or placebo (Control Group, CG).

All the patients underwent the neurological, neuropsychological and functional evaluation within the first week of their admission to the Neurorehabilitation Unit, and again after two and six weeks (T0, T1 and T2, respectively). The aim of the T1 re-evaluation was to obtain objective confirmation of the clinical observation of greater responsiveness and cooperation on the part of the patients about two weeks after the start of the drug treatment. Six weeks was chosen as the time point for the pre-discharge follow-up evaluation (T2) as this corresponds to the average length of a stroke inpatient's rehabilitation unit stay.

All the patients had an electrocardiogram and underwent a complete laboratory assessment (routine biochemistry), including renal and hepatic function tests, at T0, T1, and T2. In the first week after the start of selegiline intake, blood pressure and heart rate were monitored three times a day: in the morning, in the early afternoon and in the evening; thereafter, these parameters were recorded according to routine clinical practice at least twice a day.

All adverse events (reported by the patients or observed by the investigators) were recorded.

Patients in both groups received standard rehabilitation care, which was started on their admission to the Neurorehabilitation Unit and included physiotherapy (a one-hour session per day, six days/week), cycle/arm-ergometer training (a 30-minute session per day, five days/week), and occupational therapy (a one-hour session per day, three days/week).

A follow-up examination at six months after discharge was scheduled (T3).

2.4. Drugs and dosing

The study drug was selegiline, given as 10 mg tablets (CHIESI Farmaceutici S.p.a., Parma, Italy). The control group received, as placebo, a galenical preparation, identical in taste, size and appearance to the study drug. The patients received selegiline or the corresponding placebo for six weeks. The administration of the study drug started as soon as the diagnosis of stroke had been confirmed and the patient's eligibility had been verified.

The selegiline dose or placebo was taken once a day in the morning, two hours after breakfast, i.e. at about 10.00 a.m.