Early fluoxetine treatment of post-stroke depression
A three-month double-blind placebo-controlled study with an open-label long-term follow up

Abstract Objective Poststroke depression is a frequent psychiatric complication after stroke that may have strong negative impact on rehabilitation therapy and functional recovery. This study was conducted to show the efficacy and safety of early treatment with the selective serotonin reuptake inhibitor fluoxetine in post-stroke depressed patients. Methods This double-blind, randomized placebo-controlled study was of patients within two weeks after stroke. Moderate to severe depressed patients (determined by Hamilton Depression Scale (HDS) > 15, the Beck Depression Inventory (BDI) and the Clinical Global Impression (CGI) Scale) were randomized to receive either 20 mg/d fluoxetine or placebo for 3 months. Beside the psychiatric assessment, patients were evaluated by use of the Scandinavian Stroke Scale (SSS), the Mini-Mental-State-Examination (MMSE) and the Barthel-Index (BI). An open-label long-term follow up was done 18 months after the initial assessment. Results 54 depressed patients of an inpatient population of 242 consecutive stroke patients aged 25 to 85 years entered the trial within the first two weeks post-stroke. 50 patients completed the trial per protocol. The initial severity of depression was comparable in the two groups (mean baseline HDS score 32.8 in the fluoxetine vs. 30.3 in the placebo group), as were neurological symptom severity and demographic parameters. Significant improvement was seen in both groups within 4 weeks of treatment, whereas no advantages of fluoxetine could be observed at this time. This indicates a high degree of spontaneous recovery during early rehabilitation therapy. BDI scores of patients treated with fluoxetine further decreased until the follow-up at 12 weeks, whereas the scores increased again in the placebo group. This depressive relapse of the placebo patients after the end of most rehabilitation efforts was evident at a long-term follow-up 18 months after inclusion, when patients who had been treated with fluoxetine were significantly less depressed. No side effects of fluoxetine treatment were detected. Conclusions The advantages of fluoxetine were obvious at the follow-up 18 months after inclusion, but could not be demonstrated within the first three months of controlled treatment. The multitude of therapeutic efforts that take place in the early phase of rehabilitation might have facilitated spontaneous recovery from depression and might have hindered benefits of antidepressant treatment to become obvious. Fluoxetine treatment was well tolerated and safe.

Key words stroke · depression · fluoxetine treatment
Introduction

In spite of the high incidence of stroke and in spite of the high prevalence of depressive disorders following stroke [3, 4, 8, 15, 20, 26, 31, 35], few studies have been conducted so far indicating effective therapeutic interventions in post-stroke depression (PSD). On the one hand, this is particularly astonishing, as dramatic negative consequences of depressive disorders after stroke were found in many studies: depressed mood after stroke was associated with a poorer outcome of rehabilitation therapy [16, 24, 28, 34], with cognitive impairment [15, 16], with a markedly reduced quality of life of patients [5, 12, 18, 33] and their caregivers [19], and not at least with an increased risk of subsequent mortality in a 10-year follow-up [25]. On the other hand, the lack of therapeutic evidence is partly due to difficulties to diagnose validly both depression and antidepressant treatment effects after stroke: a considerable number of patients suffers from cognitive impairment and/or aphasia, which make a valid diagnosis impossible. Furthermore, many of the clinical symptoms of depression are nonspecific in elderly people, which causes underdiagnosis in post-stroke depressive states [13].

The first controlled treatment trials showed the advantage of tricyclic antidepressants [21, 22]. However, the adverse effects of tricyclic antidepressants cannot be ignored and limit their use especially in old patients with multiple disorders. Fortunately, a broad variety of new, well tolerated antidepressants has been introduced in recent decades, which offer new therapeutic possibilities even in patients difficult to treat. Beside a study of citalopram [2], a recently published controlled study was the first to show the advantages of the SSRI fluoxetine in early post-stroke depression [36]. A limitation of this study was the small number of included patients; it was concluded that the results should be replicated to prove efficacy and safety of the drug.

In this double-blind, placebo-controlled study with an open-label long-term follow-up, we evaluated effects of the SSRI fluoxetine in post-stroke depression. Fluoxetine has been successfully used without serious adverse effects in psychiatric patients, and advantages of fluoxetine over maprotiline and placebo were reported in a controlled study focusing on rehabilitation therapy [10]. In this study not only depressed subjects were included, indicating that fluoxetine may generally facilitate recovery in post-stroke patients undergoing rehabilitation. The need for early recognition and treatment of post-stroke depressed patients has often been emphasized [4, 13, 24]. Therefore we decided to start treatment as early as possible after stroke, because we expected to find positive treatment effects as regards better recovery in activities of daily living during rehabilitation.

Methods

Patients

Patients were recruited from all consecutive patients admitted to St.-Pölten General Hospital or to the Neurological Hospital Maria-Theresien-Schlössel following acute stroke from 1 June 1998, until 31 December 1998 (7 months). Thromboembolic stroke or intracerebral haemorrhage were verified by computed tomography. Patients were included if clinical evaluation, which was performed by senior clinical psychiatrists (S.F., E.G.), indicated moderate or severe depression, as measured by a Hamilton Depression Scale Score > 15. More than mild communication deficits and/or cognitive impairment (Mini Mental State Examination < 20) was an exclusion criterion, as were relevant diseases of the CNS (subarachnoid bleeding, cerebral tumour, thrombosis of the venous sinus), or previous degenerative or expansive neurological disorders (e.g., hydrocephalus, multiple sclerosis, amyotrophic lateral sclerosis). The study protocol was approved by the local ethics committee, and informed consent was obtained from every patient before inclusion into the study.

Measures

A neurological examination was performed at the beginning of the study, assessing the Scandinavian Stroke Scale (SSS) [32] and the Rankin Scale [29]. Patients were assessed two weeks after admission and again at follow-ups 1 month and 3 months after inclusion. The examinations undertaken included Mini-Mental State Examination [11], the Barthel-Index [23], Hamilton Depression Scale (HDS) [14] (which had to score > 15), Beck’s Depression Inventory (BDI) [7], and the Clinical Global Impression [6]. Blood samples were taken to exclude impairment of liver or renal excretion function at each examination, as well as other relevant adverse effects. After 1½ years, patients were visited in an open-label naturalistic follow-up and assessed using the SSS, HDS, BDI, and CGI.

Drug Protocol

The treatment period lasted 12 weeks. Medication was given in a single morning dose. All patients were randomly assigned to either fluoxetine or placebo treatment by the drug company independently of the research teams and the study centres. The randomization code list was generated by a computer program in a random permuted block design for each centre. The medication for this study was supplied by Lannacher Heilmittel, Lannach, Austria. Fluoxetine and placebo were supplied in identical capsules in coded boxes, neither patients nor relatives, clinical examiners nor nursing staff were aware of the drug treatment being given. The outcome of treatment was measured after 4 weeks: if the patient did not respond to the treatment (HDS > 13), the dose was doubled. Double-blind treatment was continued for further 8 weeks. Patients then were offered to continue fluoxetine treatment for relapse prevention.

Sample Size Estimation

Based on previously observed data, the standard deviation of the primary outcome measure, i.e., the change in HDS after 4 weeks of treatment was estimated at 6. A difference of 5 in the average change in HDS was considered clinically relevant. Given these assumptions the sample size calculation revealed 24 patients per group were required to detect this relevant difference with a power of 80% at a significance level of 5%.