Clinical Pathways in Neurorehabilitation

Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial.

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ABSTRACT

BACKGROUND: Hemiplegia and hemiparesis are the most common deficits caused by stroke. A few small clinical trials suggest that fluoxetine enhances motor recovery but its clinical efficacy is unknown. We therefore aimed to investigate whether fluoxetine would enhance motor recovery if given soon after an ischaemic stroke to patients who have motor deficits.

METHODS: In this double-blind, placebo-controlled trial, patients from nine stroke centres in France who had ischaemic stroke and hemiplegia or hemiparesis, had Fugl-Meyer motor scale (FMMS) scores of 55 or less, and were aged between 18 years and 85 years were eligible for inclusion. Patients were randomly assigned, using a computer random-number generator, in a 1:1 ratio to fluoxetine (20 mg once per day, orally) or placebo for 3 months starting 5–10 days after the onset of stroke. All patients had physiotherapy. The primary outcome measure was the change on the FMMS between day 0 and day 90 after the start of the study drug. Participants, carers, and physicians assessing the outcome were masked to group assignment. Analysis was of all patients for whom data were available (full analysis set). This trial is registered with ClinicalTrials.gov, number NCT00657163.

FINDINGS: 118 patients were randomly assigned to fluoxetine (n=59) or placebo (n=59), and 113 were included in the analysis (57 in the fluoxetine group and 56 in the placebo group). Two patients died before day 90 and three withdrew from the study. FMMS improvement at day 90 was significantly greater in the fluoxetine group (adjusted mean 34·0 points [95% CI 29·7–38·4]) than in the placebo group (24·3 points [1·9–28·7]; p=0·003). The main adverse events in the fluoxetine and placebo groups were hyponatraemia (two [4%] vs two [4%]), transient digestive disorders including nausea, diarrhoea, and abdominal pain (14 [25%] vs six [11%]), hepatic enzyme disorders (five [9%] vs ten [18%]), psychiatric disorders (three [5%] vs four [7%]), insomnia (19 [33%] vs 20 [36%]), and partial seizure (one [<1%] vs 0).

INTERPRETATION: In patients with ischaemic stroke and moderate to severe motor deficit, the early prescription of fluoxetine with physiotherapy enhanced motor recovery after 3 months. Modulation of spontaneous brain plasticity by drugs is a promising pathway for treatment of patients with ischaemic stroke and moderate to severe motor deficit.

FURTHER DETAILS

Patients who had an acute ischaemic stroke within the past 5–10 days that caused hemiparesis or hemiplegia were prospectively enrolled. The primary outcome was the mean change in FMMS score between inclusion (day 0) and day 90. FMMS is an index that is widely used for assessment of motor recovery after stroke. The motor domain ranges from a score of 0 (flaccid hemiplegia) to 100 (normal movement), with 66 points for the upper limb and 34 points for the lower limb; each item is rated as not, partly, or fully performed. All motor assessments were made by a physiotherapist at day 0 (baseline) and then 30 days and 90 days after enrolment. Secondary endpoints were NIHSS, modified Rankin scale (mRS), and MADRS with all scores measured at baseline, day 30, and day 90. Mean progression in FMMS total score from baseline to day 90 was significantly higher in the fluoxetine group than in the placebo group after controlling for centre, age, history of stroke, and FMMS score at inclusion. The gain was significant for both the upper (fluoxetine: 24·2 on average, placebo: 11·8) and the lower limb scores (fluoxetine: 12·2 on average, placebo: 10·1). The adjusted mean FMMS total score was significantly higher at day 90 in the fluoxetine group than in the placebo group. Independence in activities of daily life, measured by use of mRS, improved during treatment in both groups, but at day 90 the proportion of independent patients (mRS scores 0, 1, or 2) adjusted for centre, age, history of stroke, and mRS score at baseline was significantly higher in the fluoxetine group than in the control group (34% in the fluoxetine group vs. 11% in the placebo group; p=0·021)

Occurrence of depression during the 3 months was significantly lower in the fluoxetine group than in the placebo group, suggesting that fluoxetine when given early after the stroke can prevent depression: The distribution of the MADRS scores did not differ significantly between the fluoxetine and control groups at inclusion or at day 90, whereas the adjusted mean change in MADRS scores between day 0 and day 90 was significantly lower in the fluoxetine group than in the placebo group. Moreover, the frequency of depression was significantly higher in the placebo group (17 [29%] patients) than in the fluoxetine group (four [7%] patients; p=0.002).

INTERVIEW

Q1: Professor Chollet, regarding the patient selection in your study, to whom would the results apply?

CF: In the FLAME trial, patients had ischemic stroke, moderate to severe motor deficit and no other symptoms or condition that could interfere with motor evaluation. We showed that motor deficit was improved with fluoxetine. Other neurological symptoms were not considered. So patients with ischemic stroke and moderate to severe motor deficit appears to be the appropriate target.

Q2: It seems that fluoxetine treatment had a more pronounced effect on arm motor control as compared to leg motor control. Is fluoxetine a drug for arm recovery after stroke (and less so for stance and gait)? If so, why would that be?

CF: I agree that the magnitude of FMMS upper limb motricity improvement appears greater. This should be related to one main point: in the FMMS, upper limb scores vary between 0 and 66/100, lower limb scores between 0 and 34/100. So, it can be assumed that a motor improvement of the upper limb is amplified by the score. There is no particular reason for the drug to be more active on upper or lower limb.

Q3: Looking at the modified Rankin Scale data it appears that the fluoxetine treatment changed primarily the rate of those who have "moderate disability" (mRS 3 = requiring some help, but able to walk without assistance) to those who have "slight disability" (mRS 2 = unable to carry out all previous activities, but able to look after own affairs without assistance). Is that fair to say? If so, is there a subgroup of patients who benefited from fluoxetine (e.g., might patients with moderately severe or severe disability not benefit)?

CF: All patients had moderate or severe motor deficit (mean FMMS< 20 in both groups). Moreover mRS scores at the beginning were mainly 4 or 5 (see table 1). So it is not true that patients scoring 1 or 2 after treatment were scoring 3 at the beginning. They all started from 4 or 5 and some of them with fluoxetine made a greater progression than those with placebo.

Q4: There was a considerable impact of fluoxetine on the prevention of post-stroke depression. This might by and large have been the cause for a more positive rehabilitation process and oucome. Do you agree?

CF: Patients were not depressed when they were included in the study. So this is not a study on post stroke depression. However it is true that depression occurred in 4 cases with fluoxetine and in 17 in the placebo group. All these patients (4 + 17) received antidepressants and were included in the final statistical analysis. So the effect is still present with 17 patients from the placebo group treated with antidepressants. Moreover, when patients with occurring depression are removed from the statistical analysis, the difference between the two groups persists. So the Fluoxetine effect in FLAME study has nothing to do with depression. Nevertheless, it is likely that Fluoxetine has a mood effect on non depressed patients. This could affect attention, motivation... and patients might consequently have better participated in rehabilitation procedures. So we think that Fluoxetine acts both on motor system directly as it has been showed previously, and works also on more transversal shared neuronal networks that support attention or motivation.

CLINICAL PATHWAY COMMENT

Fluoxetine prescribed for 90 days, starting within a few days after an acute ischemic stroke in non-depressed hemiparetic patients with moderate to severe motor deficits showed a considerable impact in this study. Motor recovery, especially for the arm was enhanced, depression prevented, and ADL competence promoted. The drug was well tolerated.

Since fluoxetine has no longer a patent, the costs for the treatment might be considered moderate. Among trials that evaluated any medication-induced enhancement of recovery after stroke this double-blind placebo-controlled RCT demonstrated a remarkably favourable effect. If the results could be corroborated by further trials a relevant treatment option could result.

For the time being, several questions remain to be addressed:

- Who would most benefit from a prescription? What are the patient characteristics that make the medication-induced enhancement of recovery after stroke likely?
- What are the main effects of the drug (e.g., mood, arm motor control) that eventually promote ADL competence?
- How long does a prescription enhance recovery of function? Do we need to treat patients for 3 months, shorter periods, or longer?

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