COMPARISON OF FUGL-MEYER SCORE BETWEEN PATIENTS WITH ACUTE THROMBOTIC INFARC STROKE TREATED WITH STANDARD MEDICATION AND FLUOXETINE

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ABSTRACT

Fluoxetine is an inhibitor of serotonin (5-HT) reuptake, increases activation in executive motor areas of healthy subjects. Acute single dose 20 mg administration will increase extracellular 5-HT level in frontal cortex. Fluoxetine also inhibit calcium influx in smooth muscle vessels. All of that will increase cerebral blood flow and serotonergic transmission in motor cortex. The objective of the research is to prove benefits of combination treatment (standard, physical treatment and fluoxetine) than standard treatment on improving motor deficit in cerebral infarction patient. The study was performed at neurological patient in ward A Dr. Soetomo Hospital from February 12th, 2009 until May 12th, 2009. The study sample was acute cerebral infarction patients that fulfilled both inclusion and exclusion criteria. By using prospective single blind randomization, we performed motor examination (with motor Fugl-Meyer scoring) on both groups before and after treatment. The comparison result was analyzed by Mann-Whitney text. There are median motor Fugl-Meyer scale improvement in both groups on day 5th, but the improvement is better in fluoxetine group statistically significant (p=0.025). Time of administration didn’t influence on treatment effects. Fluoxetine administration beside standard treatment could increase motor outcome (motor Fugl-Meyer scale) in acute cerebral infarction patients (onset < 72 hours) significantly. (FMI 2014;50:100-103)

Keywords: fluoxetine, serotonin, motor system, cerebral infarction

INTRODUCTION

Stroke is one of the global causes of permanent disability (Windle & Corbett 2005). There are many strategies involved that are performed to stimulate and fasten the process of reorganization, such as therapies like physical rehabilitation, pharmacology, and environmental ones. Neuroprotective and tissue plasminogen activator (t-PA) have several limitations on their usage on stroke cases (Windle & Corbett 2005). Although there is much evidence that shows that serotonin is involved in motoric functions, the hypothesis of serotonergic modulation on post-stroke motoric improvement is still controversial. Study that is performed on healthy volunteers shows that a single dosage of fluoxetine on an acute phase can modulate and help the reorganization of cerebral motoric activity. Previous research shows that fluoxetine acts on motoric...
system by closing the calcium channel. The closure of the calcium channel will activate the binding of 5-HT with several motoric system receptors (Pariente et al 2001).

Fluoxetine also acts as a selective inhibitor of serotonin reuptake (selective serotonin reuptake inhibitor – SSRI), which is highly specific, safe, and often-used on neurologic cases, especially on post-stroke depression. The drug can be used to increase serotoninergic transmission; it can also penetrate the Blood Brain Barrier (Ungvari et al 1999, Pariente et al 2001). Fluoxetine also increases growth factor and several other proteins related to plasticity, like brain-derived neurotropic factor (BDNF), phosphorylated cAMP response element binding (pCREB) that has a neurogenesis function. The benefit of fluoxetine for post-stroke depression is no longer doubt. However the benefit of fluoxetine on post-stroke motoric function repair is still not clear (Windle & Corbett 2005). The Fugl-Meyer score on the fifth day after the stroke occurs can already predict 74.25% functional motoric score 6 months post-stroke (Duncan et al 1992, Swayne et al 2008). Six months post-stroke motoric condition is an optimal condition that can be achieved by stroke patients, because after 6 months, there won’t be any significant improvements. The objective of the research is to prove the theory that suggested that fluoxetine can help the process of reorganization in the brain and increases locomotors activity through serotoninergic transmission. Therefore, it is hoped that it can repair the motoric function score that is examined through the Fugl-Meyer scale.

MATERIALS AND METHODS

This research was a prospective study, single blind randomization using patient with the acute thrombotic stroke at Neurology Department of Dr. Soetomo hospital from the 12 February to 12 May 2009 which includes meet the inclusion and exclusion criteria. The inclusion criteria of this research were an acute ischemic stroke patients with first attack by clinical signs and symptoms as well as the results of the CT scan of the head without contrast, on the onset of less than 72 hours, with a unilateral motoric deficit, the age of 40-80 years, GCS of 456, Fugl-Meyer score that was more than 55. The exclusion criteria were the presence of other neurologic abnormalities in the brain, an allergic fluoxetine, severe depression, increased hepatic enzymes, renal failure, sepsis, drug abuse, and other antidepressant therapy. This research has already received permission eligibility from the ethical committee of Dr. Soetomo Hospital. Motoric strength was examined using the Fugl-Meyer Motoric Scale on the control group and the fluoxetine group before and after the therapy. The result is analyzed using the Mann-Whitney test.

RESULTS

The characteristic distribution of the research’s subjects can be seen in Table 1.

Table 1. The characteristics of several variables of research subjects of the control group and fluoxetine

<table>
<thead>
<tr>
<th>No</th>
<th>Variable</th>
<th>Control Mean</th>
<th>SD</th>
<th>Fluoxetine Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age (Years)</td>
<td>58.21</td>
<td>9.88</td>
<td>54.89</td>
<td>8.12</td>
<td>0.208</td>
</tr>
<tr>
<td>2</td>
<td>Stroke Onset (Hours)</td>
<td>30.32</td>
<td>22.13</td>
<td>16.38</td>
<td>13.59</td>
<td>0.039</td>
</tr>
<tr>
<td>3</td>
<td>Blood Pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systolic (mmHg)</td>
<td>167.42</td>
<td>27.61</td>
<td>170.93</td>
<td>20.00</td>
<td>0.928</td>
</tr>
<tr>
<td></td>
<td>Diastolic (mmHg)</td>
<td>95.76</td>
<td>13.7</td>
<td>100.37</td>
<td>8.077</td>
<td>0.71</td>
</tr>
<tr>
<td>4</td>
<td>GDA (mg/dl)</td>
<td>149.30</td>
<td>95.445</td>
<td>137.56</td>
<td>69.208</td>
<td>0.94</td>
</tr>
<tr>
<td>5</td>
<td>Albumin (mg/dl)</td>
<td>3.76</td>
<td>0.5606</td>
<td>3.89</td>
<td>0.40837</td>
<td>0.3</td>
</tr>
</tbody>
</table>

On the fifth day after the fluoxetine was given or placebo, a Fugl-Meter motoric scale was re-performed, which can be seen in Table 2.

Tabel 2. The Fugl-Meyer motoric scale score of the subjects of the control group and fluoxetine on the first day and the fifth day after the medication

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Med</th>
<th>Min</th>
<th>Max</th>
<th>Fluoxetine Med</th>
<th>Min</th>
<th>Max</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motoric Fugl-Meyer Day 1</td>
<td>78</td>
<td>56</td>
<td>94</td>
<td>73</td>
<td>57</td>
<td>95</td>
<td>0.228</td>
</tr>
<tr>
<td>Motoric Fugl-Meyer Day 5</td>
<td>84</td>
<td>57</td>
<td>99</td>
<td>92</td>
<td>43</td>
<td>100</td>
<td>0.025</td>
</tr>
<tr>
<td>Delta Motoric Fugl-Meyer</td>
<td>3</td>
<td>0</td>
<td>12</td>
<td>11</td>
<td>0</td>
<td>43</td>
<td>0.000</td>
</tr>
</tbody>
</table>

The motoric function improvement can be seen in Figure 1. On the fifth day after fluoxetine or placebo was given, a re-scoring of the HDRS scale was performed (Table 3). On the depression level analysis of the research subjects, the researcher classifies the depression condition into three categories: constant, worsens, improving. This is done to examine the effects of fluoxetine on the depression level of the subjects related to the changes of the Fugl-Meyer scale. On the third table, it can be seen that the fluoxetine group, there are more subjects that are improving compared to the control group.
Fluoxetine has two effects on the brain tissue with a case of ischemia, a direct and indirect repair of the blood vessels. The direct effect of fluoxetine is inhibiting the calcium channel of the cerebral artery’s smooth muscle. This will trigger the vasodilation of the cerebral blood vessel (Ungvari et al 1999). The indirect effect of fluoxetine also acts on the closure of calcium channel. The closure of the calcium channel will create an activation of the binding of 5-HT with several receptors with roles on the motoric system (Pancrazio et al. 2004). The binding of 5-HT1B/1D and 5-HT2C receptors, which is abundant in the motor cortex is estimated to be responsible for activating the locomotor system that repairs motoric function. The binding of the receptors depends on the closure of the calcium channel (Wurtman & Zervas 1974). The repair of brain blood flow is evidenced Neuroimaging (fMRI) research which shows ipsilateral hiperactivity of the primary motor cortex due to a lesion and hipoactivity in the bilateral cortex due to a lesion and hipoactivity in the bilateral
areas of cerebellum, caudate nucleus, secondary somato sensory cortex area, inferior bilateral parietal area of BA40, and contra lateral lesion of the premotor cortex after fluoxetine administration (Pariente et al 2001, Loubinoux et al 2002). The mechanism that underlies the fMRI founding is the ability of serotonin to stimulate pyramid cells that have high density in the primary motor cortex. The hipoactivity founding of the cerebellum shows that serotonin has an inhibiting effect on purkinje cells of the cerebellum through the stimulation of interneuron inhibition (Lugaro cell) (Pariente et al 2001, Pleger et al 2004). Pariente also claimed that fluoxetine administration without rehabilitative physical therapy wills not generate a significant motoric repair (Pariente et al 2001). Therefore, fluoxetine therapy is given simultaneously with physical training therapy.

Researchers are trying to prove the beliefs that suggested that motoric repair that happens after the administration of fluoxetine on stroke patients are caused by mood, concentration, and attention repair as well as a feeling of energized that correlates with depression improvement (Stahl 2008). Researchers are attempting to eliminate all of the effects of the depression confounding variables on the control and treated groups by performing randomization during the allocation of research subjects. Therefore there wouldn’t be any significant difference of depression level of subjects (HDRS) between the control and treated group (p > 0.05). From the examination after the fifth day, the fluoxetine group is shown to have a better improvement of depression level (59.3%) compared to the control group (30.3%). On the fluoxetine group, there is only a small amount of subjects that have a worsening state of depression (7.4%) compared to the control group (27.3%). The difference between the two groups is quite significant (p = 0.041). This result is corresponding to the research by Wiart et al (2000) who examined the benefit of fluoxetine administration as early as possible on stroke patients. He stated that an early administration would repair the patient’s depressive state. However, this result still requires further analysis through other researchers trying to obtain the correlation between depressions healing with the motoric improvement on stroke patients.

CONCLUSION

The addition of fluoxetine on a standard medication for acute thrombotic stroke patients with onsets less than 72 hours would significantly improve the functional motoric system (measured by the Fugl-Meyer motoric scale).

REFERENCES


