Comparison of Brain-derived Neurotrophic Factor Level in Depressed Patients Treated with Fluoxetine and Sertraline

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Abstract

BACKGROUND: The brain-derived neurotrophic factor (BDNF) is the main neuronal growth factor in the brain that regulates neurogenesis, neuronal maturation, synaptic formation, and plasticity. Studies showed BDNF level decreased in depression and the administration of anti-depressant drugs increased BDNF level. In this study, we used fluoxetine and sertraline, which are Selective Serotonin Reuptake Inhibitor (SSRI) but had a different mechanism in influencing the BDNF levels.

AIM: The purpose of this study was to compare the effect of fluoxetine and sertraline administration to the BDNF level in depressed subjects.

METHODS: This study was conducted at Wahidin Sudirohusodo Hospital, Makassar, Indonesia and its affiliates from January to February 2019. Twenty outpatient subjects were diagnosed with depression based on DSM-V. The subjects were either antidepressant naïve or dropping out of antidepressant therapy for at least 3 months since the last administration. Blood samples from each subject were taken by consecutive sampling, and BDNF levels were analyzed before and after administration of fluoxetine and sertraline for 6 weeks. Furthermore, Hamilton Depression Rating Scale (HDRS) scores are measured before and after administration.

RESULTS: The BDNF serum was significantly increased by 100.6% (p < 0.001) from the baseline level in the fluoxetine group and 75.4% in the sertraline group. HDRS score was decreased by 39.5% (p < 0.001) in the fluoxetine group and 30.1% in the sertraline group after 6 weeks of administration.

CONCLUSION: This study suggests that fluoxetine was superior to sertraline in increasing the BDNF level in depression.

Introduction

Depression is a major contributor of the overall global burden of disease that affects over 300 million people worldwide. Clinical manifestations of depression include one or more persistent episodes of sadness and anhedonia within 2 weeks, with changes in appetite, disturbed sleep patterns, decreased energy levels, decreased physical concentration and activity, feelings of worthlessness, guilt, and thoughts or suicidal behavior. Other symptoms are mostly secondary to changes or have a relationship with these changes. Most of these disorders tend to recur and the occurrence of individual episodes is often associated with significant life events or stressors [1], [2].

Depression is a serious public health concern. The World Health Organization states that depression is in the fourth rank of diseases in the world. Depression affects about 20% of women and 12% of men in a lifetime [2], [3]. Based on the results of basic health research in Indonesia (Riskesdas 2013), the prevalence of mental disorders showed by symptoms of depression and anxiety is 6% for those aged ≥15 years, or about 14 million people [3], [4].
BDNF is the main neuron growth factor in the brain that regulates neurogenesis, neuronal and survival, synaptic maturity, and plasticity. Low BDNF levels are found in the brains of individuals who experience depression, especially in areas (hippocampus, prefrontal cortex, and amygdala) that showed atrophy in depressed patients. Decreased BDNF levels are also found in the blood of patients who are depressed, and this can be reversed by treatment. Negative environmental effects such as psychological stress can also reduce BDNF levels in the hippocampus. The direct impact of antidepressants on BDNF had also been reported, infusion of BDNF into the hippocampus has an antidepressant-like effect. These findings provide hope that increased BDNF levels in certain brain areas targeting the pathways involved can be a new strategy in the prevention and treatment of depression. Research on genetic expression in humans had shown that BDNF is highest in the cortex, hindbrain, and midbrain [14], [15], [16]. Serum BDNF levels are normal in response to some antidepressant therapies [17], [18].

Fluoxetine is metabolized to norfluoxetine, whose activity is the same as fluoxetine in taking 5-HT. Elimination of half-life of norfluoxetine is longer, which is 4–16 days, while fluoxetine is only 4–6 days. Fluoxetine works to inhibit the reuptake of serotonin neurotransmitters. The structure and activities of each SSRI are different. The chain R-enantiomer of fluoxetine antagonizes the 5-HT 1c receptor at almost micromolar concentrations. Its clinical relevance is unknown. The therapeutic dose of fluoxetine is 20 mg–80 mg/day [10], [11].

Serotonin neurons in the midbrain raphe nucleus have autoreceptors on the soma (5-HT1A) and a terminal region (5-HT1B) stimulated by an acute increase in 5-HT neurons. Sertraline decreases the activity of the sympathetic nervous system. Decreased sympathetic response provides an anxiolytic effect that is associated with the stimulation of 5-HT1A receptors. Sertraline reaches a peak plasma level between 6 and 8 h after administration. Range of therapeutic doses is 50–200 mg/day [12], [13], [14].

Statistical analysis
Data analysis was computed using SPSS version 22. Statistical analysis was performed using Mann–Whitney and Wilcoxon signed-rank and results were statistically significant with p < 0.05.
Results

Based on the statistical analysis, the data included the characteristics and distribution of the subject. The study group involved 20 depressed patients who met the inclusion criteria. The subjects comprised 10 subjects who treated with fluoxetine 20 mg every 24 h orally and 10 subjects treated with sertraline 50 mg every 24 h orally. HDRS scores and BDNF levels were measured at the beginning and after 6 weeks of the treatment.

The age of the subjects in the study group was between 20 and 45 years, with mean from fluoxetine group was 35.20 years with standard deviation of 5.31 years and sertraline group was 36.70 years with standard deviation of 7.96 years, whereas the age in the control group was between 19 and 27 years with mean 22.90 years and standard deviation of 2.69 years (Table 1).

| Variable     | Group  | n  | Mean  | Std. Deviation |
|--------------|--------|----|-------|----------------|
| HDRS 0       | Fluoxetine | 10 | 16.75 | 1.11 |
|              | Sertraline | 10 | 3.10  | 0.66 |
|              | Control   | 10 | 13.17 | 3.82 |
| BDNF 0       | Fluoxetine | 10 | 4.70  | 1.11 |
|              | Sertraline | 10 | 4.63  | 1.11 |
|              | Control   | 10 | 13.17 | 3.82 |

Table 1: Comparison of HDRS and BDNF before and after 6 weeks of treatment of fluoxetine and sertraline

Changes in HDRS scores after 6 weeks of therapy compared to baseline were as follows: In the fluoxetine group, there was a significant decrease from 17.20 to 10.40 or a decrease of 39.5% (p < 0.01); and in the sertraline group, there was a significant decrease from 16.30 to 11.40 or a decrease of 30.1% (p < 0.01). Changes in BDNF expression after 6 weeks of therapy compared to baseline were as follows: In the fluoxetine group, there was a significant increase from 4.70 to 9.43 or an increase of 100.6% (p < 0.01); and in the sertraline group, there was a significant increase from 4.56 to 8.00 or an increase of 75.4% (p < 0.01) (Table 4).

Discussion

Most literature stated that depression often occurred at a young age, with an average age between 20 and 40 years [1], [2], [3]. Gender of the subjects was mostly women at 10–25% in both groups, but the distribution of men and women in both groups was not different. Various studies showed that women were twice compared to men with lifetime prevalence in women was 10–25% and in men was 5–12%. This was under the literature stating that women were more often exposed to environmental stressors and the threshold for stressors was lower in women than men and also related to hormones in women at the time of premenstrual, postpartum, and postmenopause [2], [3], [4]. Distribution of education in the two groups was not different.

Comparison of HDRS scores before administration of fluoxetine and sertraline was significantly higher in the depressed group than in the control group. Comparison of BDNF levels before administration of fluoxetine and sertraline was lower in the depressed group than in the control group. In depressed patients who were given fluoxetine therapy and whose changes were better with increased BDNF levels in the fluoxetine group than in the sertraline group. Comparison of HDRS scores after 6 weeks of therapy, there was a decrease in both the fluoxetine and sertraline groups. In fluoxetine, the results of HDRS score show a decrease, as does the BDNF level which is increasing. Anti-depressant drugs can increase BDNF levels by activating the 5-HT receptor so that
serotonin levels in the presynaptic increase and activating the serotonin receptor. Periodic monitoring of BDNF levels is needed to maintain neurons from damage due to repetitive stressors.

Conclusions

The researchers concluded that there was a decrease in HDRS scores and an increase in BDNF levels in depressed patients treated with fluoxetine and sertraline. The fluoxetine group was superior in decreasing HDRS scores in depressed patients compared to the sertraline group, and the fluoxetine group was superior in increasing the BDNF levels in depressed patients compared to the sertraline group. Further study is needed to see the effect of other antidepressant groups to the level of BDNF.

Authors’ Contributions

All the authors were involved in the conception of the study STL, NAM, RN, and SS to the interpretation of the research findings and contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

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