

The Effect of Selective Serotonin Reuptake Inhibitor Drugs on Serum Interleukin-6 Levels among People with Depression

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ABSTRACT— Depression is a disorder of mood resulting in the reduction of productivity, an increase of suicide risk, and decreasing quality of life. The pathogenesis of depression might be associated with interleukin 6 (IL-6) that increases among depressed patients. Serotonin selective reuptake inhibitors (SSRI) agents have been widely used for the treatment of depression, but no reference discussed the comparison of the level of IL-6 among patients who were treated with SSRI and non-SSRI. This study determines the difference in serum IL-6 level among depressed patients were treated with SSRI and non-SSRI antidepressants. A cross-sectional study among 79 (54 SSRI groups and 25 non-SSRI groups) participants who were diagnosed with depression, having the medication with an antidepressant for at least 1 month were performed. The subjects then asked for venous blood collection for the serum IL-6 level examination. The comparison of serum IL-6 level was analyzed using the Mann-Whitney U Test. Our results demonstrated that there are no significant differences in the demographic, clinical characteristics, and serum IL-6 level among SSRI compared to the non-SSRI group ($p=0.605$). In conclusion, there is no significant difference in serum IL-6 levels among SSRI-treated depression patients compared to the non-SSRI groups.

KEYWORDS: Antidepressant, Depression, IL-6, SSRI.

1. INTRODUCTION

Depression is a disorder of mood characterized by a reduction of mood, desires, excitement, and energy for daily activities, with the consequences such as loss of a job, reducing productivity, increasing suicide risk, and decreasing quality of life [1]. The World Mental Health survey conducted in 17 countries found that 1 of 20 people had a history of depression. The Ministry of Health's Basic Health Research (RISKESDAS) also demonstrated that the prevalence of depression in Indonesia among ages more than 15 years old is approximately 14 million people or 6% of the total population [2], [3]. The pathogenesis of depression has been widely carried out over the past and various underlying changes have been made for therapeutic interventions [4]. The role of inflammatory cytokines such as interleukin 6 (IL6) in the pathophysiology of depression is challenging, and it may be contributed to the improvement of depression. The previous study demonstrated that there was an increase of inflammatory cytokine such as IL-6 levels both in central and peripheral tissues among depressed patients, and a meta-analysis study revealed that IL-6 serum levels were significantly higher in depressed patients. This evidence suggests that IL-6 may play a major role in the inflammatory responses in depressed patients [5], [6]. The increase of IL-6 might induce an increase of neurotransmitter levels and improve the dysregulation of neuroendocrine, resulting in the recovery of depression [7]. The effect of IL-6 on the response to antidepressant agents is still controversial. The level of IL-6 can be a predictor of the response of the antidepressant agents such as serotonin selective reuptake inhibitors (SSRI) or another antidepressant (non-SSRI) therapy in depressed patients [8]. There is no reference discuss regarding the comparison of the level of IL-6 among depressed patients treated with SSRI

and non- SSRI. This study determines the differences in IL-6 serum levels in depressed patients receiving SSRI antidepressant compared to the non-SSRI. This study was a cross-sectional study conducted at the General Hospital Dr. Kariadi Semarang Indonesia, General Hospital Tugurejo Semarang Indonesia, Diponegoro National Hospital Semarang Indonesia, and Permata Medika Hospital Semarang Indonesia, the period of January to May 2019. The participants were patients who diagnosed with depression based on the medical records, obtained using consecutive admission sampling method, with inclusion criteria: 18 years of age or more, willing to take the study, taking the antidepressant regularly for at least 1 month, non-smoking, and the exclusion criteria: taking narcotics, psychotropic substances, and other addictive substances, suffering from the severe and chronic physical illness, and psychotic disorders. The serum IL-6 levels were measured from venous blood from the median cubital vein, examined in the Prodia Clinical Laboratory Semarang Indonesia using Human IL-6 Immunoassay Quantikine HS ELISA (R&D Systems, Inc the US). The preparation of samples was performed according to the insert kit from the manufacturer.

Demographic and clinical data including sex, age, level of education, marital status, occupation, level of income, type of stressor, duration of therapy, and the other physical illness were classified based on the type of antidepressant into two groups: The SSRI group, who received SSRI antidepressant (n=30) and the non-SSRI group, for who received another antidepressant (n=30), then analyzed using SPSS software version 17.0 for Windows, (IBM Corporation, US). Categorical scale data such as sex, occupation, marital status, genetic factor, level of education, level of income, type of stressor, history of psychiatric disorders among family, history of previous psychiatric disorders, and the history of other physical illness were cross-tabulated using the Chi-square test. While for numerical scale data such as age was analyzed with a two-independent samples T-test, and the duration of treatment was analyzed using the Mann-Whitney U test because of the abnormal data distribution, and the last, the comparison of serum IL-6 levels was analyzed using the Mann-Whitney U Test. This study was approved by the Local Research Committee with an ethical clearance certificate 415/EC/KEPK/IX/2019. The subjects were given informed consent and their anonymity is preserved.

2. FINDINGS AND DISCUSSION

The involvement of inflammatory changes seems to be a centerpiece of depression pathology. Unfortunately, the inflammatory process in depression is poorly understood. Two meta-analyses demonstrated that IL-6 is the most consistently elevated cytokine in the blood of patients with depression. The IL-6 levels correlate with the severity and response of the treatment. There is no data regarding the comparison of the serum IL-6 levels in depressed patients related to the type of antidepressant received by patients. Herewith we present the evidence considering the serum IL-6 levels among depressed patients using SSRIs and non-SSRIs antidepressants. The demographic and clinical data including sex, age, occupation, marital status, genetic factor, level of education, level of income, duration of therapy, type of stressor, history of psychiatric disorders, and the history of other physical illnesses can be seen in Table 1. Table 1 demonstrated that, in this study, the participant's age is 43.59±12.86 years old. 72.2% of participants are female, and the most type of stressor is related to a primary support group (53.2%), medical conditions, and social environment (13.9% and 11.4% respectively). Regarding the use of antidepressants, most of the participants use fluoxetine (55.7%), maprotiline (20.3%), and sertraline (12.7%). The mean duration of treatment is 15.71±12.61 months. The analysis of cross-tabulation for the demographic and clinical characteristics demonstrated that there were no significant differences among most of the characteristics, except for the marital status (p=0.040). First of all, several factors are affecting the severity of depression that might be affect the outcome of therapy and correlate with the IL-6 levels. To determine the difference between these factors, we performed the cross- tabulation analysis.

Table 1. Demographic Characteristics of Participants (N=79)

Variables	Type of Antidepressant		p
	SSRI (n=54)	Non SSRI (n=25)	
	Mean \pm SD, n (%)	Mean \pm SD, n (%)	
Age (years)	43,15 \pm 12,79	44,56 \pm 13,24	0,653
Sex			
Male	17 (31,5)	5 (20)	0,290
Female	37 (68,5%)	20 (80%)	
Occupation			
Unemployed	4 (7,4%)	0 (0%)	0,561
Student	6 (11,1%)	2 (8%)	
Housewife	21 (38,9%)	13 (52%)	
Civil servant	3 (5,6%)	2 (8%)	
Private	23 (37,2%)	8 (32%)	
Marital status			
Married	44 (81,5%)	15 (60%)	0,040 [*]
Divorced alive / death	2 (3,7%)	5 (20%)	
Single	8 (14,8%)	5 (20%)	
History of psychiatric disorders among family			
Yes	3 (5,6%)	1 (4%)	1,000
No	51 (94,4%)	24 (96%)	
Level of education			
Not completed primary school	3 (5,6%)	1 (4%)	0,520
Elementary school	11 (20,4%)	5 (20%)	
Middle School	10 (18,5%)	2 (8%)	
High school	21 (38,9%)	9 (36%)	
Company	9 (16,7%)	8 (32%)	
Level of Income			
Within Minimum Wage	5 (9,3%)	0 (0%)	0,237
Below Minimum Wage	42 (77,8%)	20 (80%)	
Above Minimum Wage	7 (13%)	5 (20%)	
Duration of therapy (month)	12 (1 – 48)	12 (1 – 48)	0,936
Type of stressor			
Primary support group	27 (50%)	15 (60%)	0,242
Occupation	7 (13%)	1 (4%)	
The economy	6 (11,1%)	2 (8%)	
Education	0 (0%)	1 (4%)	
General medical conditions	6 (11,1%)	5 (20%)	
Related Social Environment	8 (14,8%)	1 (4%)	
Previous psychiatric disorders			
Yes	1 (1,9%)	2 (8%)	0,234
No	53 (98,1%)	23 (92%)	
Other physical diseases			
Yes	15 (27,8%)	11 (44%)	0,154
No	39 (72,2%)	14 (56%)	

A previous study showed that age increases the risk of depression with the consequence of an increase in IL-6 serum levels. In another study, age was related to IL-6 serum levels, the older people have higher IL-6 serum levels compared with young people. This is consistent with the study conducted among the geriatric population. The study reveals that the high level of IL-6 serum in the geriatric population is thought to have an important role in the presence of depression in this population [8]. However, in this study, we showed that there is no significant difference in age in the SSRI and non-SSRI groups ($p=0.653$). So we can assume that the chance of bias to determine the difference of IL-6 related age among both groups was elucidated. The level of serum IL-6 is also influenced by stressors especially poor psychosocial status. The demographic characteristics of our subjects demonstrated that type of stressors is mostly regarding the

primary support group. This is consistent with the previous study, that there is a significant relationship between a life event and depression, mainly due to the loss of parents (primary support group) and the loss of a partner (primary support group) [8]. However, in this study, there is no significant difference in the type of stressors among both groups ($p=0,242$). Marital status contributes to the occurrence of depression. Depression most commonly occurs in people who do not have close interpersonal relationships such as divorced, separated from their partners (primary support group). In another study mentioned that unpleasant married status such as domestic violence, stressful marriages influence the emergence of mental disorders, more severe episodes, personality disorders, and suicidal thoughts [8]. The result of this study, reveals that the marital status among SSRI and non-SSRI groups are similar ($p=0.040$). Genetic factors are an important factor in the development of mood disorders including depression. A previous study shows that the relative risk of the presence of depression is two or three times greater if there are family members with depression [9]. The result of this study, reveals that the history of psychiatric disorders among family among SSRI and non-SSRI groups is similar ($p=1.000$). Unpleasant socio-economic factors could result in depression. A previous study proofed that depression tends to be found in a person with low incomes or unemployed due to a lack of financial condition resulting in unfulfilled basic needs. The World Mental Health survey mentioned that the psychiatric conditions associated with the unpleasant socioeconomic conditions including unemployment and the difficulty in working and lack of income increases the risk of depression, which then increases IL-6 serum levels [8]. In this study, there was no significant difference in the occupation and total income among both SSRI and non-SSRI groups, $p=0.561$ for occupation and 0.237 for the level of total income).

Besides, the level of education affects the occurrence of depression. A good level of knowledge will determine good attitudes and behaviors related to their health [8- 10]. A previous study also showed that there were significant differences in IL-6 serum levels in the immune system with susceptibility to conditions of repetitive psychosocial stress. In other studies, it was found that IL-6 serum increased in susceptible mice compared to the tough mice when facing adaptation difficulties with psychosocial stress [9]. Our results showed that there was no significant difference in the education levels and also prior psychiatric disorders in SSRI compared to the non-SSRI group. IL-6 has many functions in the immune system and can act as an inflammatory or anti-inflammatory cytokine [11]. IL-6 also can act as a neuronal growth factor that causes neurite development and nerve regeneration [12] depending on the level of circulating IL-6, neuron type, age, and immune status, and inflammatory conditions. The IL-6 serum levels in healthy conditions have the value of 4 pg/ml, in certain conditions such as chronic diseases, autoimmune, and other physical disease comorbidities, IL-6 serum levels increase at the level of 10 pg/ml to 1000 pg/ml [13], [14]. Our cross-tabulation result demonstrated that there is no significant difference in the history of physical disease among both groups ($p=0.154$).

Table 2. The Differences in serum IL-6 levels in the SSRI and Non-SSRI groups (N=79)

Antidepressants	IL-6 serum levels (Median (Min-Max))	p
SSRI (n=54)	4,04 (1,00 – 55,71)	0,605
Non SSRI (n=25)	3,17 (0,85 – 19,67)	

The data analysis then was continued to determine the comparison of serum IL-6 levels among SSRI and non- SSRI group. The result of the analysis can be seen in Table 2. Finally, we found that there is no significant difference in serum IL-6 levels among depressed patients receiving antidepressant therapy in SSRI and non- SSRI groups ($p=0.605$). in contrast, a meta-analysis by Hannestad *et.al*, stated that there was a significant relationship of antidepressants to serum IL-6 levels, specifically the SSRI. SSRI group has the potential to have a strong effect on the improvement of plasma cytokines [8], [15]. A cross-sectional study

using antidepressant therapy (fluoxetine) for 2-4 weeks, showed that IL-6 serum levels improved at the level of 11.62 pg/ml. Another study also found that IL-6 serum levels of depressed patients ie 10.1 pg/ml compared to control subjects ranging from 1.8 pg/ml. In the literature mentioned IL-6 serum levels in healthy conditions are 4 pg/ml [16]. Our study does not analyze the detailed type of antidepressant, so we cannot conclude whether there is an influence of the type of antidepressant on IL-6 levels. There are still many variables that may affect the levels of IL-6, such as the dose of the drug, other types of drugs that are also consumed, body mass index (BMI), that do not include in this study, so further study is needed to determine the effect of those variables on the IL-6 level among depressed patients.

5. CONCLUSION

There is no significant difference in IL-6 serum levels among depressed patients receiving antidepressant therapy in SSRI and non-SSRI.

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