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FLOUXETINE IMPROVED INTRAVAGINAL EJACULATORY LATENCY TIME THROUGH DECREASED LEVELS OF INTERFERON-GAMMA AND INCREASED LEVELS OF SEROTONIN IN PATIENT WITH PREMATURE EJACULATION

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ABSTRACT

Pathophysiology of premature ejaculation (PE) is very complex because it is associated with many factors, which can be grouped into biological factors and psychological factors. Various diseases have been found correlate between psychological factors and biological factors through cytokines, one of which is IFN-g (IFN-γ). IFN-γ affect indolamine dioxygenase enzyme (IDO) and decrease levels of serotonin. Low levels of serotonin leads to PE. The purpose of this study was to prove the relationship of serotonin and IFN-γ in pathophysiology of PE.

This study was designed as a pretest-posttest double-blind cross-over control group design. Patients with PE were divided into 2 groups: control group and treatment group. Treatment group received flouxetine 20 mg for 30 days. Then the control and treatment groups were crossed after passing a 14-days washout period. Previously as a control group to treatment group and received flouxetine 20 mg per day for 30 days. Before and after treatment in each group was examined the levels of serotonin and IFN-γ.

Of the 26 subjects, each group there was 13 subjects. Flouxetine 20 mg per day for 30 days increased serotonin levels were significantly ($p < 0.05$), and decreased levels of IFN-γ were significantly ($p < 0.05$). Increased levels of serotonin and decreased levels of IFN-γ was significantly associated with improvements (intravaginal ejaculatory latency time) ejaculation in PE patient.

From these results it can be concluded that PE occurs because decreased levels of serotonin. Decreased levels of serotonin are associated with increased levels of IFN-γ.

Keywords: PE, Serotonin, IFN-γ.

INTRODUCTION

Pathophysiology of PE is still an interesting subject to be investigated, because of the many factors involved in the phatophisyologies and the mechanism is very complex. These factors can be grouped into two factors: biological and psychological factors, but how the interrelated of these factors still need to do further research. In some disorders in addition to PE, it was found the relationship between serotonin and cytokines, one of which is IFN-γ. The problem is how these factors are interrelated in the pathophysiology of PE?

Regarding the mechanism of ejaculation there were consists of two phases, namely emission and expulsion phases. In general it can be explained ejaculation occurs because the stimulus was triggered by a stimulus such as glan penis and tactile stimuli from various areas in the cerebral cortex. The disorders of ejaculation are PE, retrograde ejaculation, delayed ejaculation and an ejaculation.[1]

PE is the most common ejaculation disorders. Ejaculation occurs very rapidly, from the moment of penetration of penis into the vagina until ejaculation is very short, the inability to control ejaculation, and the distress in question, and spouse. The time required from the time of the penetration penis into the vagina until ejaculation is called intravaginal ejaculatory latency time (IELT). To measure the time specified in the study less than or equal to 2 minutes.[2-5]

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Serotonin is one of the neurotransmitter involved in ejaculation.[6] The role of serotonin in the ejaculation can be explained by several studies that have been carried out. Research in this field using antidepressants, one of which is the Selective Serotonin Re-uptake Inhibitors (SSRIs). As research conducted by one researcher using one type of SSRI is flouxetine 20 mg. The result was flouxetine can fix PE. Flouxetine combined with tadafil can significantly prolong the intravaginal ejaculatory latency time (IELT) in patients with PE. Other studies also use flouxetine 20 mg for 8 weeks, showed improvement ejaculate reaches 68%.[19] With another type of SSRI paroxetine 20 mg is the research done by measuring intravaginal ejaculatory latency time (IELT) was also found to provide improvements to PE, and found no side effects.[16]

Then recently with dapoxetine, which is one type of SSRI with short half life and rapid onset of action, so it can be given about 3 hours before sexual intercourse, have a very high concern. One of the studies regarding the efficacy and tolerability of dapoxetine in PE, involving 2614 patients found that dapoxetine may improve ejaculatory control and sexual enhancement and found no serious adverse events.[17,21]

Later research found a relationship of serotonin and cytokines in various types of disorders outside the PE. Serotonin activation likely contribute to inflammation in blood vessels during aterogenesis.[13] One of the cytokines interferon can lead to decreased levels of serotonin because interferon can increase serotonin re-uptake and interferon can decreased serotonin synthesis via the mechanism of indoleamine 2,3-dioxygenase enzyme (IDO).[18,23] Interferon can also cause decreased levels of tryptophan which are precursors of serotonin.[9]

Serotonin is derived from the amino acid tryptophan. Metabolism may be through two ways, namely: first through the IDO enzyme, which will transform tryptophan into kynurenin, and second through tryptophan hydroxylase enzymes, which will transform triptopan into serotonin. IDO enzyme can be activated by IFN-γ. In the event of increased levels of IFN-γ, the IDO enzyme will become more active so tryptophan be metabolized via the enzyme IDO becomes kynurenin, and the other is due to reduce of serotonin.[9,23]

From the description above and the research results can be formulated in several ways, among others, that serotonin is a neurotransmitter that plays a role in PE, low serotonin levels lead to reduced inhibition and ejaculation occur rapidly. There was a correlation of anxiety, IFN-γ and serotonin in patients with PE.[20] That is why researchers want to know the correlation between IFN-γ and serotonin in pathophysiology of PE. In this study, flouxetine was applied to prove this hypothesis.

METHODS

In order to prove the hypothesis on the research carried out with experimental study design is double-blind cross-over posttest pretest-control group design. Flouxetine used in this study, because of the difficulty to get dapoxetine. Subjects were randomly divided into 2 groups, one group will receive placebo 1 capsule/day for 4 weeks (30 days), and one other group will receive flouxetine 20 mg/day for 4 weeks (30 days). Subjects were evaluated every 4 weeks. At the end of week 4 all subjects examined its ejaculation, serotonin levels, levels of IFN-g and anxiety. Then all the subjects experienced during the 2-week washout. Once that was carried out cross (Cross over) against a group of research subjects. Who got the placebo group received flouxetine and vice versa. Examination performed on the first day when screening, day 30, day 45 and day 74.

PE is checked through a structured interview based on the DSM IV criteria. Timing or intravaginal ejaculatory latency time (IELT) ≤ 2-minute interview conducted by examination carried out 4 times. First time start, both on day-30, the third on day 45, four on day 74. Severity measured by PE Severity Index (PESI).

Examination anxiety was carried out using the Taylor Manifest Anxiety Scale (T- MAS). Examination was performed at baseline anxiety (h0), day-30, day-to-45, and day-74. Examination of IFN-g (IFNγ) performed at the Prodia Laboratory Denpasar. Blood samples were collected from venous blood cubiti, this examination using ELISA method. Examination conducted at the Laboratory of blood serotonin Prodia Denpasar. Venous blood samples were taken from cubiti, for the storage of more than 6 hours can be done with a temperature of 2-8 degrees Celsius. To protect the serotonin made by the addition of 0.1% ascorbic acid solution. Examination conducted by the method of Ultra Sensitive Enzyme Immunoassay (EIA).

RESULTS

This study involved 26 of PE men patients aged less than 50 years. The patients are divided into 2 (two) groups, namely the control and treatment groups, so that each numbered 13 people. After 30 days followed by a 14-day washout phase, then was proceed with the examination of levels of serotonin and IFN-γ. Washout performed during 14 days.

Serotonin

Independent t-test analysis showed significance difference between control group and treatment group. Means of serotonin in treatment group was 165.28±71.35 and in control group was 195.29±95.29.

Analysis of significance with independent t-test showed that the value t = 0.918 and p = 0.368. It means that the means levels of serotonin in the two groups did not differ (p > 0.05).

Analysis of treatment effects were tested based on the means levels of serotonin between the groups after the treatment is given. The results of the analysis of significance with independent t-test showed that the means levels of serotonin in treatment group was 205.03±113.93 and the means of control group was 102.52± 90.72. Significance analysis showed that the value t = 2.54 and p = 0.018. It means that the average levels of serotonin in the two groups differ significantly (p < 0.05).

IFN-γ

Comparability of test aims to compare the mean levels of IFN-γ. The results of the analysis of significance with independent t-test showed mean treatment group was 0.96 2.71 and the means levels of control group was 1.09 2.03. Analysis of significance with independent t-test showed that the value t = 0.14 and p = 0.889. in both groups did not differ (p > 0.05).

Analysis of treatment effects were tested with independent t-test showed that mean of treatment group was 0.15 ± 0.09 and the average levels of control group was 0.33 ± 0.17. Analysis of significance with independent t-test showed that the value t = 3.32 and p = 0.004. in both groups were significantly different (p < 0.05).

Period effects and residual effects

After 30 days and then go into the second period. In the second period carried the cross, where the control group who had previously received treatment with placebo have given flouxetine 20 mg daily for 30 days, whereas the treatment group receiving a placebo for 30 days as well. Between the first and second period there is a 14-day washout phase. To determine the effect of the first period of the second period and the period analyzed the effect of residual effects.

Serotonin levels

The analysis aims to determine the effects of period effects that arise related to cross-over design with two periods, namely the provision of treatment to compare the mean difference in change in serotonin levels of the first period to the period between the two treatment groups. The results of the analysis of significance with independent t-test showed that the mean difference in change in serotonin levels of the treated 47.86 ± 140.13 the average control group was -76.07 ± 195.28. Analysis of significance with independent t-test showed that the value t = 1.36 and p = 0.198. It means that the period effect serotonin levels in the two groups did not differ (p> 0.05).

IFN-g (IFN- γ) t-test showed that the mean levels of IFN-γ in control group was 1.23± 2.84, and mean levels in treatment group was -0.33 ± 2.02. Analysis of significance with independent t-test showed that the value t = 1.18 and p = 0.261. It means levels of IFN-g in both groups did not differ (p > 0.05).

The analysis aims to determine the residual effects of residual effects of treatment are still relevant in the second period cross-over design comparing the mean changes in serotonin levels in the two periods between treatment groups. The results of the analysis of significance with independent t-test showed that the average change in serotonin levels of the treated group was -39.52 ± 99.50 average control group was 52.86±93.28. Analysis of significance with independent t-test showed that the value t = 0.26 and p = 0.800. This means that the residual effects in both groups did not differ (p> 0.05).

Effect of Flouxetine for Levels of IFN-g (IFNγ) and Serotonin Levels in PE

To determine the effect of giving flouxetine to decrease levels of IFNγ and increase levels of serotonin and PE, tested by logistic regression test. Based on the analysis found that increased levels of serotonin have the greatest impact on improving PE with the odds ratio (OR) = 2.025 (95% CI: 1.006 to 3.045) and p-value = 0.011. This suggests that elevated levels of serotonin have an influence on the improvement of PE were significantly (p <0.05)

To determine the effect of giving flouxetine to improve PE was analysis using Chi-Square test is based on 2 x 2 cross table. Based on the analysis found that in the treated group of 8 people (61.54%) had improvement of PE and the remaining 38.46% is still suffering from PE, whereas in the control group there were only 2 people (15.38%) who experienced improvements in ejaculation 84.62% of early and still suffer from PE. With chi-square test found that there is a relationship between flouxetine with improvements in patients with PE were significantly (p <0.05).

DISCUSSION

In this study it was found that the average age of patients with PE were in the range of 20-50 years. Analysis of significance with independent t-test showed that the probability of significance (p) for the age variable is p = 0.075. This means that the average age in both groups did not differ (p > 0.05). This suggests that age is negligible effects on changes levels of IFN- γ and levels of serotonin. The mean long-married people with PE in this study were 6.62 ± 6.39; lowest 1-year and the longest 25 years (p = 0.075). The mean long-married in treatment group was 8.46 ±

8.10 and mean of the control group was 4.78 ± 3.47. No statistically significant influence (p = 0.145) for other factors.

In the study conducted in Korea with questionnaire spread through the internet, with a lifespan of 20 years to 59 years found that there was no difference in the prevalence of PE in a particular age group.[22] Thus it can be argued that long-married factors are negligible effects on IFN-γ and serotonin.

Cholesterol and blood sugar factor in this study were also analyzed. It was found that total cholesterol levels averaged 191.08 ± 37.25 and blood sugar levels on average were 97.92 ± 10.12. Analysis of significance with independent t-test showed that the probability of significance (p) for blood sugar and total cholesterol, respectively p = 0, 490, and p = 0.208. It means that blood sugar and total cholesterol in both groups did not differ (p > 0.05). This suggests that these variables are negligible influence on changes in IFN-γ and serotonin levels.

IFN-γ

The results of the analysis of significance with independent t-test showed that mean of treatment group was 0.09 ± 0.15, and average levels of control group was 0.17± 0.33. Analysis of significance with independent t-test showed that the value t = 3.32 and p = 0.004. in both groups were significantly different (p<0.05). Based on the analysis of Spearman's correlation coefficient obtained between the levels of IFN-γ and improve of PE is r = 0.582 and p = 0.002 (p <0.05).

IFN-γ has a negative correlation with serotonin. In this study found the correlation coefficient was r = -0.718 with p = 0.001. It mean decrease levels of IFN-g significantly correlated with an increase levels of serotonin. IFN-γ can enhance IDO enzyme that causes a decrease levels of serotonin in several types of viruses and cancer who received interferon therapy.

Levels of Serotonin in PE

Serotonin had been studied and can be cited as the cause of PE. In the present study also found that about 61, 54% of patients with PE improved after being given flouxetine 20 mg/day for 30 days. Analysis of significance with independent t-test showed that the value t = 2.54 and p = 0.018. This means that the average levels of serotonin in the two groups differ significantly (p <0.05). Based on Spearman's correlation test, it was obtained that r = - 0.664 and p = 0.001. This suggests that elevated levels of serotonin associated with improvements in PE.

The role of serotonin in PE has been widely studied. Such research is conducted using one type of SSRI is flouxetine 20 mg. The result was flouxetine can fix PE. Other studies also use flouxetine 20 mg for 8 weeks, showed improvement ejaculate reaches 68%.

Effect of Flouxetine for IFN-γ, Serotonin and Improvement of PE

Improvement of PE is related to elevated levels of serotonin (r = -0.664 and r = 0.001, decreased levels of IFN-g (r = 0.582 with p = 0.002). Flouxetine can significantly decreased levels of IFN-γ for 4 weeks and improved of PE (r = 0.582 and p = 0.002).

In this study it was found that the group given flouxetine 20 mg / day for 30 days, 8 out of 13 people (61.54%) improved its PE. With chi-square test found that there is a relationship between flouxetine 20 mg/day for 30 days with improvement in patients with PE were significantly (p <0.05).

Other studies with flouxetine 20 mg for 8 weeks also provide improvements of about 68%. With another type of SSRI sertraline 50 mg during the first week has given approximately 68.75% improvement.

With logistic regression test was found that increased levels of serotonin have the greatest impact on improving PE with the odds ratio (OR) = 2.025 (95% CI: 1.006 to 3.045). This suggests that increased levels of serotonin have the strongest influence on the improvement of PE were significantly (p <0.05).

Side effects that occurred in this study only one person is decreased sex drive. Nevertheless need to get the attention and good explanations and understandable. Because some side effects found in the use of SSRIs are nausea, insomnia, somnolent, anxiety, sexual dysfunction and decreased sexual drive an orgasm.

CONCLUSION

Based on research results and the above discussion it can be concluded as follows 1) Flouxetine can decreased levels of IFNγ in patients with PE, 2) Flouxetine can increased serotonin levels in the blood of patients with PE; 3) Decreased levels of IFN-g (IFNγ), and increased levels of serotonin associated with improvements of PE.

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