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The effect of adding folic acid to drug regimen (citalopram) in response to treatment of depressed patients

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ABSTRACT

Since the optimum level of folic acid is required for normal functioning of the brain and body, this study aimed to determine the effects of adding folic acid to the diet (citalopram) was conducted in response to the treatment of patients with depression. This study is a double-blind clinical trial. The study population included all patients with depression referred to Farabi Hospital in 2014. Patients in the study and control groups were examined. In the experimental group the therapeutic dose of citalopram with folic acid were administered, but citalopram and placebo in the control group. Beck questionnaire was used to evaluate the response to treatment. The results showed that the response to treatment levels was statistically significant in the sense that the response to treatment in the study group was faster, but the two groups did not achieve statistically significant results. To determine the effect of folic acid in response to treatment of patients with depression and the need for adding it to the usual anti-depression drugs requires further studies with longer durations.

Keywords: depression, response to treatment, cognitive disorders, folic acid

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INTRODUCTION

The mood is a pervasive and sustained emotional state that inner feeling and the behavior and understanding of one of world affects the external manifestation of the people's affection. The mood may be normal, high or low [1].Examples include low mood and depression, with one or more major depressive episodes without a history of Mani, mixed or Hypomania defined as at least 2 weeks and must have at least four symptoms from list that includes changes in appetite and weight, changes in sleep and activity, lack of energy, feelings of guilt, difficulty thinking and decision-making, recurrent thoughts of death and suicide [2].

It was recently shown that inpatients with mood disorders such as both major depression and manic phase havelow folate plasma concentration, and several clinical trials have shown that adding vitamin to be effective antidepressants [3].

Folic acid is one of B vitamins, which when absorbed into its active form tetra hydrofolate, participates as carrier of one-carbon units in purine metabolic reactions such as the synthesis of nucleotides and Purine nucleotide synthesis and Pyrimidine[4,5].

Folate is necessary for the proper functioning of the central nervous system and mood. Since folate plays an important role in the sub-units of one-carbon metabolism (the process of methylation and synthesis neurotransmitters) in the central nervous system [6, 7, 8], a sharp decline in this vitamin leads to memory loss, decline of mental function and depression [9].Reduced folate levels also is associated with the severity of depression and periods of depression [6,10,11].Vegetarian foods like vegetables, legumes and fruits are excellent sources of

folate, but also there are a lot of folate in animal foods. Heating results in folate destruction, and bran of the grain separates it [4]. In some studies, increased plasma hem cysteine level as a co-factor in the pathology of mental illness has been identified [10,11,12,13,14], but not in all of them[9].Increased hem cysteine can lead to damages in the central nervous system, cardiovascular and neurological systems, and a reduction in neurotransmitters [6].

The active metabolite of folate is required for methylation of hem cysteine to produce Methionine (it is One of biochemical processes involved in production of neurotransmitters) [8]. Since in the training centers of Kermanshah University of Medical Sciences there has been no study in this regard, researchers aimed to determine the effect of supplementation of folates in depressed patients in this study.

MATERIALS AND METHODS

Research Methodology

The study is double-blind clinical trial that examined the effect of adding folic acid to the therapeuticdiets in treating patients with depression who referred to Kermanshah Farabi Hospital. This research was registered on the Iranian Registry of Clinical Trials with the code of 2013033112825N2 IRCT (www.irct.ir) The sampling was made convenience. Inclusion criteria included criteria for major depressive disorder based on DSM-IV, the Iranian sample, having age more than 18 years, and exclusion criteria included patients with mental retardation based on clinical diagnosis or intelligence test (IQ <70),patients who needed ECT therapy and physical control due to the severity of symptoms based on clinical assessment by a psychiatrist, any contraindications for folic acid consumption, folic acid-related tumors, the possibility of pregnancy, drug abuse or drug dependence since 3 months prior to the survey, the risk of suicide and the need for other measures, weighing less than 30 kg, schizophrenia, and neurological and medical disorders (seizure disorders and epilepsy), Gastrointestinal disorders (stomach cancer, sprue, chronic diarrhea, celiac, absorption disorders related to liver disease - biliary, etc.), sensitivity to folic acid, kidney disease, taking any dietary supplements and medications, such as calcium, vitamin B, vitamin and D, chronic infection, cases of anemia. In this study, patients were divided into two groups. The control group patients were given citalopram at therapeutic dose (60 mg) with placebo, and experimental group were given drug citalopram with folic acid at dose of 5 mg.

Maximum replication was observed between study and control groups. Study groups were selected as the people in the control group based on the variables listed in the demographic characteristics (age, education, occupation, marital status, etc.). School of Pharmacy Department was responsible for the preparation of placebo and a psychiatrist determined drug program. Patients in the study were measured by Beck questionnaire in 5 times intervals: during the clinical interview, zero and two weeks later, and then 3,2,1 months later, and at end of the study, to evaluate symptoms, cure rate, and the side effects of the drugs. A specialist carried out the rate of compliance.

RESULTS

Descriptive findings show the mean pre-test experimental groups 7.03 ±3.707, and the amounts in the control group 7.59 ± 35.76. Grades 4, respectively, for the experimental and control groups, 3.09 ± 22/15, 5.65 ± 23.66 respectively (Table 1).

Table1. The mean depression score in both experimental and control groups

Group	pre-test	Posttest1	Posttest2	Posttest3	Posttest3
	standard deviation ± Mean	standard deviation ± Mean	standard deviation ± Mean	standard deviation ± Mean	standard deviation ± Mean
Test	7.03 ± 37.70	36.74±6.80	29.74±6.29	4.86±22.38	15.22±3.09
Control	7.59 ± 35.76	7.62±35.50	7.01±31.56	6.45±28.80	5.65±23.66

To evaluate the effect of adding folic acid to the drug regimen (citalopram) in response to treatment of depressed patients repeated measures analysis of variance was used. Table 2 shows the results of the experimental group and the control group in terms of a linear combination of the pre-test and post-test scores of the difference (pilot intervention).

Table2. The results of the experimental group and the control group in terms of a linear combination of scores of difference between the pre-test tests

Resources	Test	Value	F	Df1	Df2	Sig.	Eta
Level	Lambda Wilkes	0.098	169.49	4	56	0.001	0.92
Level *Group	Lambda Wilkes	0.45	16.77	4	56	0.001	0.54

With respect to the F (16.77), which corresponds to the level of interaction with the group, the results showed that in the experimental and control groups, at least one of the difference variables there are significant differences.

Table 3: analysis of variance between groups

Resource	Test	Sum of square	df	Mean of square	F	Sig.	Eta
Level	Green House Geysers	13294.09	2	7808.18	514.77	0.001	0.90
Level *Group	Green House Geysers	1188.83	2	698.16	46.03	0.001	0.44

The F value equals to 46.03, above the level P<0.001,and is significant; it represents significant change in the control and experimental groups. In fact, this is a significant imbalance between the two groups shows the regression slope. Continued analysis of variance with repeated measures is shown in Table 5 for depression. Table 4 shows the linear and quadratic levels of depression, in the table of F for linear trend that is significant 1146.49, which indicates that depression scores in subjects in a linear process have significant, meaningful change, is also in the process of non-linear and zigzag. The results of the linear trend subjects at different levels are according to Table 4.

Table4. Continued analysis of variance with repeated measures

Test	Sum of square	Df	Mean of square	F	Sig.	Eta
Linear	1146.49	1	1146.49	62.73	0.001	0.51
Nonlinear	29.17	1	29.17	6.98	0.01	0.11

Table5. The results of the linear trend subjects at different levels according to the group

Sources	Sum of square	df	Mean of square	F	Sig.	Eta
Group	475.94	1	475.94	2.71	0.10	0.04

Table 5 shows linear trend subjects at different levels of the dependent variable in the experimental and control groups are the same and there is no significant difference between the two groups.Changes in depression in the pre-test and post-test are shown in Figure 1 below.

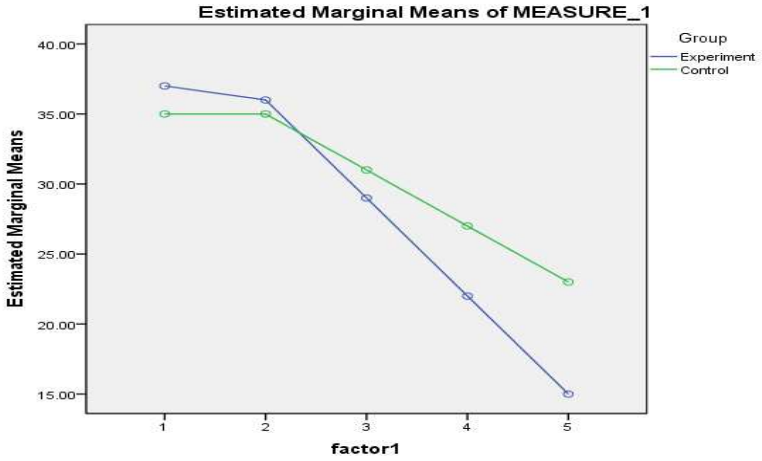

Table6. Continued analysis of variance with repeated measures in the experimental group

Test	Sum of square	df	Mean of square	F	Sig.	Eta
Linear	10909.42	1	10909.42	416.14	0.001	0.93
Nonlinear	359.50	1	359.50	57.59	0.001	0.66

This table shows the linear and quadratic levels of depression is significant in this table which F is the 416.14 for linear trend, and this indicates that depression score Afterwards groups in a process a significant change is linear, non-linear and zigzag also in the process of significant change. Post hoc Bonferroni test results also suggest that there is a significant difference between all levels of depression in the experimental group (pretest, posttest 1, posttest 2, posttest 3, posttest 4).

CONCLUSION

As the results show a decline in test scores in the study group was bigger compared to control group. The Beck Depression Inventory scores in the experimental group in the third test were comparable with the fourth post-test scores in the control group. This means that in patients who received folic acid response to therapy increased after one month, incomparison to the control group. According to the study, although there were statistically significant

differences in response to treatment during the intervals of scoring, but there was no significant result between the two groups. Christenson's result was similar to this. Christenson and colleagues, in their clinical trial had studied 900 adults between 60 to 74 years old in 2008 in Australia. In their study one group of patients received antidepressants, 400 micrograms of folic acid, and vitamin B12, while the other group was on100 microgram Vitamins, antidepressants and placebo. Self-reported uses of antidepressants were recorded during the 2years of study.

Participants in the study were studied using the PHQ-9 questionnaire at 6 weeks, 6 and 12 and 24 months. According to the study, there is little evidence that folic acid and vitamin B12 have an effect to increase antidepressants responses. According to the researchers, the selected dose of folic acid is considered as one of the factors affecting the results of their research [15]. Morris and colleagues in their review article in 2008 entitled (folate and depression, unipolar) in Texas, found that serum levels of folate in the depressed patients is lower than non-depressed people. The results showed that low levels of folate were associated with reduced response to antidepressant drugs, and increased floats strengthen the response to antidepressants [16]. According to Morris, one of the reasons for the lack of meaningful research results between the two groups was the improper use of folic acid in the study, because the study results are based on self-reported folic acid consumption. Almedia and colleagues in West Australia in a double-blind clinical trial, found 273 people with a reduced risk of depression for the effect of B vitamins in 2010. In this study, the folic acid group (mg2) received vitamin B6 (mg25) and vitamin B12 (mg0.5) for up to 5-10 years. The results of the experimental group that received vitamin B compared with a control group that received placebo showed a reduction in the risk of depression [17].

Another possible reason for the lack of significant results in the two groups could be related to duration of treatment with folic acid in the study group. According to a survey of Almedia a few months of folic acid, seems to be a very short period. To determine the effect of folic acid in response to treatment of patients with depression and the need to prescribe it along with the usual anti-depression drugs, we recommend further study with increased time of folic acid. Should be cautious in generalizing the findings, because this study was conducted among patients at referred to Farabi Hospital for the treatment of depression; it is recommended future research to be done in the broader community.

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