Increase in the folate level can decrease the intensity of disorder in patients with depression who use citalopram: a randomized clinical trial

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Abstract

Background Depression is one of the most common mental health disorders, which affiliated more than four percent of world population. Several antidepressant agents, including citalopram were developed. High dose and long-term treatment with these agents along with their side effects decrease the treatment adherence. Using supplements such as acid folic is a way to increase these drug's efficacy. The aim of this study was to assess the effect of acid folic supplement and increase in blood folate level of the intensity of depression symptoms.

Methods This was a randomized-controlled clinical trial. Twenty-four patients with major depression were randomly assigned to two groups. Both groups received citalopram as their standard treatment. The intervention group received acid folic supplement (1mg/daily). The folate levels of blood, Beck's depression inventory and Hamilton depression scale scores were measured. The measurements were conducted before intervention, and in 45 and 90 days follow ups. Data were analyzed using Mann-Whitney U and Friedman tests.

Results The blood level of folate was increased for the intervention group. The Hamilton depression scale and Beck Depression Inventory Scores were reduced significantly in both groups after 90 days follow up. There were no significant differences between two groups in the reduction of depression scores. In the intervention group, the decrease of Hamilton's depression scale score was negatively correlated to the increase of blood folate level.

Conclusions The increase in blood folate level may be correlate with the decrease in depression symptoms. The use of 1mg/d supplement of acid folic was not effective in the reduction of depression symptoms in patients with major depression.

Registered in Iranian Registry of Clinical Trials (IRCT20180115038373N1)

Background

Depression is one of the most common mental health disorders worldwide [1]. It is related to high rates of mortality and morbidity [2]. The prevalence of depression worldwide is estimated 4.4 %[3]. Iran Has high prevalence of depression, and it is increasing. The estimation for depression in Iran was 4.9%, which was higher than global prevalence [3]. The literature indicates that regarding the development of antidepressant agents, the cumulative prevalence of depression remained stable. One of the reasons of this is that people with depression do not reach to their therapeutic goals [4]. Because the increase of dosage of anti-depressant agents can increase their side effects [5, 6], recent efforts have focused on increasing the effectiveness of drugs [7, 8].

Citalopram is one of the most widely used and effective antidepressants. It is used to treat mild to severe depression [9]. Numerous studies have shown its effectiveness [10, 11]. However, long-term and high-

dose use of citalopram, like other antidepressants, may reduce adherence to treatment [12]. In recent years, the use of supplements has been considered to increase the effectiveness of citalopram.

The use of supplements along with main drugs to increase their effectiveness is a controversial issue. The effects of B vitamins and vitamin D on the recovery of patients with depression who receive antidepressants were assessed in several studies. Some mice models showed that vitamins can increase the effect of antidepressants [13]. Low level of blood folate was associated with higher prevalence of depression [14-16]. Some studies assessed the effect of the folic acid supplements on the depression [17]. It has been argued that elevated blood folate levels can increase the effectiveness of citalopram, but there is no consensus on that [14, 16]. Acid folic is a safe supplement which is prescribed for several groups, but its effectiveness is not completely clear in depression. The aim of current study was to assess the effect of acid folic supplement and increase in blood folate level of the intensity of depression symptoms.

Methods

The study was a single-blind randomized clinical trial. The study was conducted at the Zanjan Haft-Tir Clinic between February 2018 to January 2019.

The minimum sample size was calculated using G*Power 3.1.9.2 (http://www.gpower.hhu.de) for repeated measure ANOVA with within–between interactions n= 24 (β = 0.80, α = 0.05, number of measurements = 3, number of groups = 2, estimated correlation between measurements = 0.3 and medium effect size f = 0.45). Thirty patients entered in the study, and twenty-four patients were evaluated at the end of 90 days. The process of the study is presented in the CONSORT diagram (Figure 1). The inclusion criteria were patient with depression, which was diagnosed by a psychiatrist and we reordered to use Citalopram 20mg/day, age above 18 years, the Beck Depression Inventory scores higher than 15 at enrolment, the absence of other psychiatric (including bipolar disorder, drug abuse) or physical illnesses and pregnancy. One psychologist examined all possible patients with inclusion criteria with Hamilton Depression Rating Scale. Study subjectsa ssigned into two parallel group, including an intervention group (acid folic 1mg/day along with citalopram 20mg/day) and a control group (citalopram 20mg/day). Random assignment was conducted using a bag containing 30 orbs, which was labeled equally to two groups (A and B). Subjects who picked orbs with label A, were assigned to intervention group and vice versa.

Measurements

Dependent variables were depression and blood folate level. They were measured at the beginning of the study, day 45 and day 90.

Depression was evaluated by Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HAM-D). BDI has 21 items, and it is a suitable scale to evaluate depression in people with age 13 and above. Each item receives a score between 1 to 3, and the sum of all item's scores (0-63) indicates the

severity of depression. BDI scores are classified as minimal (0-13), mild (14-19), moderate (20-28), and severe (29-63) depression. This scale is translated into Persian, and its validity and reliability were tested and reported in a previous study (α=0.876) (31). HAM-D is a scale which needs to administer by an expert. It has 17 items, which score between 0-4 and each subject can receive a score between 0-54. Scores below 7, 7-17, 18-24 and 25 and above indicate the absence of depression, 7- 17 mild, moderate and severe depression, respectively. The validity and reliability Persian version of HAM-D were examined in a previous study (r=0.89) (33).

Serum folate was measured by ELIZA method using Monobind kits. One hundred microliters of each sample were poured into a glass tube. Then, 50 microliters of stabilizing/releasing solution was added to the tube and mixed on Vortex for 2-3 seconds. It repeated three times for each tube. Each tube was incubated for 15 minutes at room temperature. Immediately after the addition of neutralizing solution, the tubes were mixed on the vortex for 2-3 seconds. Then at the end of the extraction, the samples were incubated for 5 minutes.

Statistical Analysis

Data was analyzed using SPSS 16. The distribution of depression scores and folate levels of two groups were assessed by Schapiro-walk test, and they did not have normal distribution. Mann-Whitney-U, Friedman's tests were used to examine the changes between two groups.

Results

From fifty-three patients who were assessed for eligibility, thirty patients had inclusion criteria and were enrolled in the study. Twenty-four patients completed all three phases of study. The demographics of study subjects are presented in table 1. The Mean ± SD of age in intervention and control groups was 31.83 ± 10.10 and 28.08 ± 6.15, respectively (p=.433).

Table 1- Demographic Characteristics of Study Subjects in two groups

Variables		Group		Test
		Intervention n (%)	Control n (%)	
Sex	Female	10 (83.3)	12 (100)	p=.478
	Male	2 (16.7)	0 (0)	
Job status	Without Job	11 (91.7)	7 (58.3)	p=.155
	With job	1(8.3)	5(41.7)	
Education	Under Diploma	2 (16.7)	3 (25)	P= .999
	Diploma	4 (33.3)	3 (25)	
	BSc	3 (25)	4 (33.3)	
	MSc	3 (25)	2 (16.7)	
Economic Status	Poor	2 (16.7)	1 (8.3)	p=0.999
	Moderate	7 (58.3)	7 (58.3)	
	Good	3 (25)	4 (33.3)	

A Friedman test was carried out to compare the folate level, Hamilton and Beck Inventory scores for the three periods (Table 2). In the intervention group, there was a significant difference between three measurements of folate levels $\chi2(2) = 15.16$, $p<.001$. Dunn-Bonferroni post hoc tests were carried out and there were significant differences between enrollment and 90-day follow-up ($p < 0.001$). In the control group, the difference between three measurements of folate levels was not significant $\chi2(2) = .667$, $p=.717$. The Hamilton scores in the intervention group decreased significantly $\chi2(2) = 17.167$, $p<.001$. Based on Dunn-Bonferroni post hoc tests, there were significant differences between enrollment with 45- and 90-days follow-ups ($p=0.024$ and $p<.01$). The decrease of Hamilton scores in the control group was also significant $\chi2(2) = 18.667$, $p<.001$ and Dunn-Bonferroni post hoc tests showed that the differences between enrollment with 45- and 90-days follow-ups were significant ($p=.003$ and $p < 0.001$). The BDI scores in the intervention group decreased significantly $\chi2(2) = 8.52$, $p=.014$. Based on Dunn-Bonferroni post hoc tests, there were significant differences between enrollment and 90-days follow-up ($p=0.024$). The decrease of BDI scores in the control group was also significant $\chi2(2) = 19.696$, $p<.001$ and Dunn-Bonferroni post hoc tests showed that the differences between enrollment with 45- and 90-days follow-ups were significant ($p=.018$ and $p < 0.001$). In the intervention group, there was a negative correlation between blood folate level and Hamilton's scores ($rho=-0.677$, $p=0.016$). In the control group, there was no correlation between blood folate level and Hamilton's scores ($rho=-0.090$, $p=0.782$).

Table 2- Comparison within and between groups of Blood folate, Hamilton and BDI Scores

Variable	Time	Group	N	Mean	Std. Deviation	Std. Error Mean	Mann-Whitney-U	Friedman	
								Intervention	Control
Blood Folate	Before Intervention	Intervention	12	6.60	2.75	.79	P=.671	P=.001	P=.717
		Control	12	7.15	3.66	1.06			
	Follow-up 45 Days	Intervention	12	9.05	3.48	1.00	p=.630		
		Control	12	8.99	5.75	1.66			
	Follow-up 90 Days	Intervention	12	15.56	8.56	2.47	p=.033		
		Control	12	8.62	4.94	1.42			
Hamilton Score	Before Intervention	Intervention	12	22.08	5.71	1.65	p=.843	P=.001	P=.001
		Control	12	22.00	5.29	1.53			
	Follow-up 45 Days	Intervention	12	13.00	5.92	1.71	p=.160		
		Control	12	9.67	4.25	1.23			
	Follow-up 90 Days	Intervention	12	9.17	4.30	1.24	p=.713		
		Control	12	8.17	4.20	1.21			
BDI Score	Before Intervention	Intervention	12	24.42	8.45	2.44	p=.198	P=.014	P=.001
		Control	12	29.58	11.36	3.28			
	Follow-up 45 Days	Intervention	12	14.33	11.04	3.19	p=.887		
		Control	12	14.00	8.73	2.52			
	Follow-up 90 Days	Intervention	12	11.83	10.08	2.91	p=.630		
		Control	12	9.75	7.39	2.13			

Discussion

The aim of current study was to evaluate the effect of acid folic supplementation on the decrease of symptoms in patients who were diagnosed with depression and were ordered to use citalopram daily. Our results showed that while the Acid folic supplementation increased the blood level of folate in the intervention group significantly, there were no significant changes in the Hamilton and BDI scores between two groups. Our results also showed that the increase in blood folate level was negatively relevant to the decrease of Hamilton's scores in the intervention group. This correlation was not significant in the control group.

Our result is in line with the studies conducted before [18, 19]. Our results were in disagreement with the results of the study of S Zahra, O Abdollah and G Narges [13] that showed that augmentation therapy by folic acid reduced the depression in patients with major depression. The dose of folic acid in our study (1 mg/d) was lower than the dose in their study (2.5 mg/d) which can explain the difference.

The result of previous studies showed that the relationship between dietary folate and depression severity significantly differed by race/ethnicity and some races benefit more [20]. The difference between our results with previous studies may be related to the dosage and response of Iranian people to acid folic supplements. Furthermore, usual food habits can affect the results.

One of the limitations of our study was lack of control over patients' foods. Patients in the control group may receive a lot of folic acid from food. The changes in level of folate in blood of patients on the control group, showed that they did not take enough folic acid from food sources. Another limitation of our study was the small sample size which reduced the generalizability of our results. Accurate follow-up and regular blood sampling of patients in large sample size is difficult.

We recommend monitoring the level of minerals and vitamins in patients with depression who receive antidepressants to achieve the best results. We also recommend future studies to compare the effect of different doses of folic acid supplementation on the depression symptoms.

Conclusion

Our results showed that low dose of acid folic supplementation can increase the level of blood folate, but it is not effective for the reduction of depression symptoms in compare to citalopram alone. The increase in blood folate level may be correlate with decrease in depression symptoms. The use of 1 mg/d supplement of acid folic was not effective for the reduction of depression symptoms in patients with major depression.

Abbreviations

BDI
Beck Depression Inventory

HAM-D
Hamilton Depression Rating Scale
ELISA
Enzyme-Linked Immunosorbent Assay

Declarations

Ethics approval and consent to participate

The protocol of the study was approved by Ethics Committee of Zanjan University of Medical Sciences (IR.ZUMS.REC.1396.246, 2018-01-02). It also is registered in Iranian Registry of Clinical Trials (IRCT20180115038373N1). Informed written consent was received from all patients. They were informed that they can reject to be in the study at any time during the study. They were also informed that all of their data will be confidential.

Consent for publication

Not Applicable

Availability of data and materials

All data will be available on request. All request should send to islambulchilar.mina@gmail.com and will be responded in one week.

Competing interests

There is no competing interest in the designing or reporting of the study.

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Authors' contributions

M.M., M.I., A.E. and H.R. wrote the manuscript draft, M.I., Y.M. and S.R. designed the study and M.M. conducted the intervention, H.R and A.P. Conducted statistical analyses. All authors reviewed the final manuscript.

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Figures

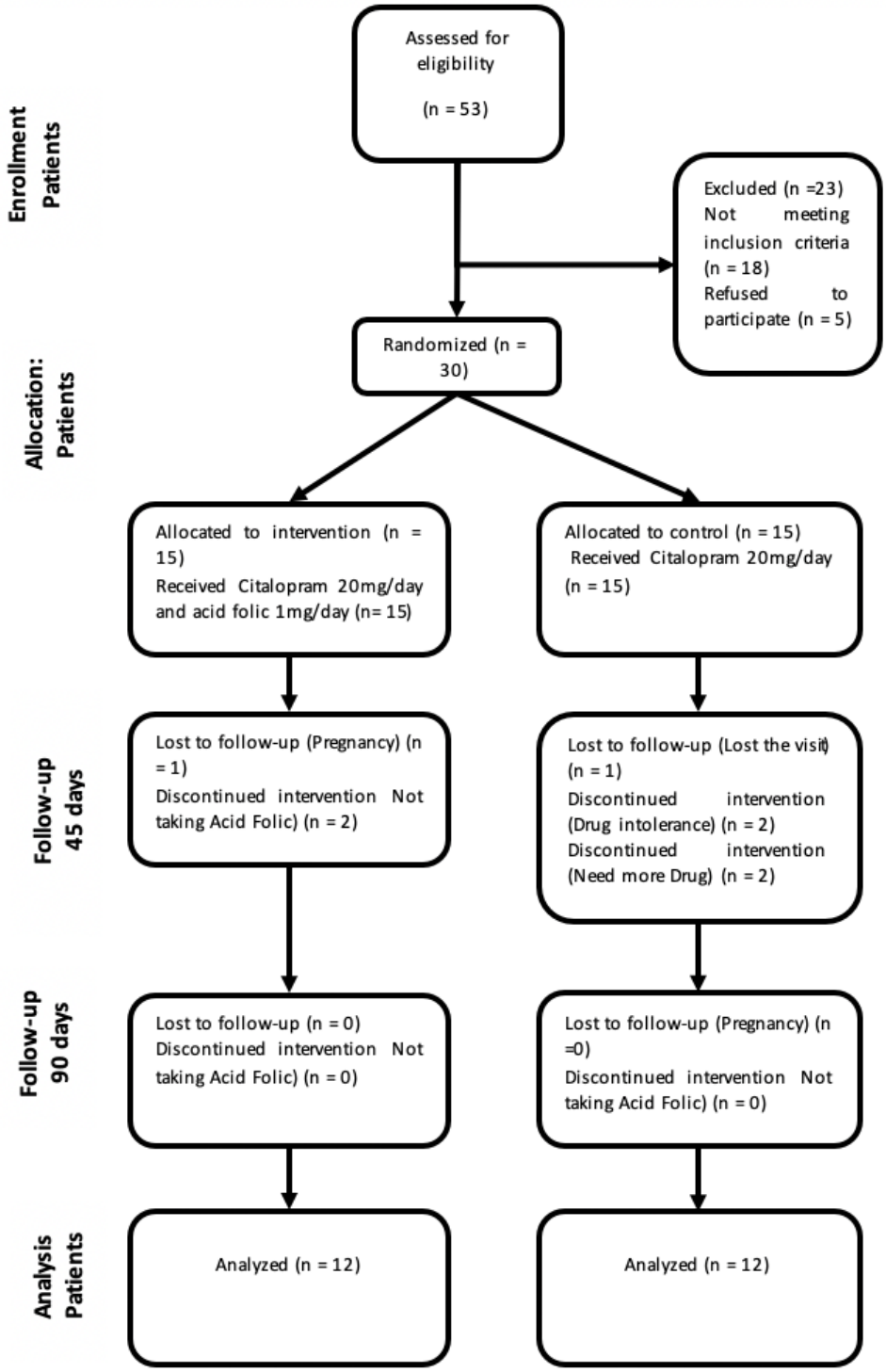

Figure 1

CONSORT diagram detailing the process of the study

Supplementary Files

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- CONSORT2010Checklist.doc