The Impact of Folic Acid on Pharmaceutical Regimen (Valporate Sodium) in Treatment of Mania

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Abstract: For proper function of body and brain it is necessary to have an optimal level of vitamin B9. Recently, studies are focused on the impact of vitamin B9 in treatment of cognitive disorders. The present research is carried out to indicate the effect of Folic Acid on Pharmaceutical Regimen and Treatment of Mania. In a double blind clinical trial two groups of patients are considered: 32 patients with BMD and 29 patients in a control group; the first group received Folic Acid and Valproate Sodium and the second group received placebo and Valproate Sodium. To assess their response to the treatment, we used young questionnaire in different times: at the beginning, after 2 weeks, after 1 month, after 2 month and after 3 month. In both trial and control group, mean scores of responses to young questionnaires declined from 26.69 and 21.38, at the beginning, to 9.59 and 16.62, after 3 month, respectively. In trial group, the reduction that we observed after 2 weeks was not significant; however, it became significant in the following points in time. The reduction in the control group was only significant after 3 month. The results show that, at the same time with similar condition of patients, the trial group showed more score reduction than the control group. It seems adding Folic Acid to Pharmaceutical Regimen of patients with Mania accelerates their respond to treatment.

Key words: Folic Acid · Cognitive Disorder · Mania · Clinical Trial

INTRODUCTION

Mood is a pervasive ongoing state felt within an individual affecting his behavior and understanding of the world around while emotion refers to external manifestation of mood. Every one may be normal, bad- or good- tempered. A normal person may experience a wide range of temperaments and different emotional states as well Kooshan and Vagheei [1]. Acute phase mania in bipolar mood disorder I is a serious medical emergency brining about undesirable social and individual consequences which needs effective diagnostic and therapeutic measures [2]. Recent researchers showed that patients with mood disorder, such as depression and mania, have low plasma folate level [3]. Folic Acid is one of the B vitamins and through absorption process it converts to its active form; tetrahydrofolate, as a carrier of one-carbon units participates in metabolic reactions such as purine nucleotides and pyrimidine synthesis [4, 5].

Folate is necessary to adjust mood and to control the function of central nervous system so lack of it leads to memory loss, reduced mental function and depression [6]. As far as the central nervous system is concerned, Folate is an important element in one-carbon units’ metabolism sub-pathway (Including methylation and synthesis of neurotransmitters) [7-9]. Vegetables such as legumes and
fruits are folate-rich foods; however, it also exists in animal food but when high heat separates it from the shell and destroys folate [4]. In many studies, increased level of plasma homocysteine is known as a cofactor in pathology of mental disorders [10-14], of course, not all of them Watanabe et al. [6]. Increasing homocysteine may damage nervous, cardiovascular and neurological systems and intensify neurotransmitters reduction [7]. To produce methionine, active folate metabolite is required for homocysteine re-methylation (A biochemical process included in neurotransmitter production) [9]. The present research is carried out to assess the impact of adding Folic Acid to regimen in treatment of patients with Mania.

MATERIALS AND METHODS

After receiving the ethics committee approval, this double-blind randomized clinical trial with placebo control was conducted in Kermanshah Farabi Hospital, a double blind clinical trial carried out on Mania patients admitted to Farabi hospital of Kermanshah. The needed subjects are selected based on Convenience sampling; at least 17 subjects should be included in each group. 65 patients with identified BID are included with the trial. Patients are divided to two case and control group, randomly. 4 subjects were removed from the study: 1 in case group because of being pregnant and 3 in control group due to severe infection (n=1) and the need for ETC treatment (n=2). Finally, the control group consists of 29 subjects and the case group consists of 32 patients. Inclusion criteria are: having DSM-IV criteria for mania disorder and +18 years of age. Exclusion criteria are: mental retardation based on clinical diagnosis or IQ test (IQ<70), patients with severe need for ETC and physical treatment based on clinical assessment, Folic Acid contraindications, Folic Acid-related tumor, the possibility of pregnancy, substance abuse or addiction till 3 month before the study, risk of suicide, the need for preventive measures, weighting less than 30 Kg, schizophrenia, medical and neurological disorders, seizure disorder and epilepsy, digestive disorders (Stomach cancer, sprue, chronic diarrhea, celiac, absorption disorders related to liver and bile disease, etc), sensitivity to Folic Acid, kidney disease, taking any dietary and medical supplements such as calcium, vitamins B and D, etc., chronic infections and any kinds of anemia.

Subjects of this study, patients with mania (Including the new cases), are divided to two control and trial groups. In order to make the situation equal, as many filters as possible are considers. The controlled variables include age, education, employment, marital status, etc. A psychiatrist ordered the medications as follows: Sodium Valproate and an atypical antipsychotic [Standard therapeutic regimen] with placebo for the control group; and the same regimen plus folic acid in a dose of 5mg daily for the trial group. The medications prescribed for the patients to use are checked by a psychiatrist. For the control group the common treatment methods (Sodium Valproate and atypical antipsychotic with therapeutic dose) with placebo is carried out, while for the trial group the common treatment method and Folic Acid with 5 Mg dose a day is prescribed.

To assess manic symptoms and rate of recovery, the Young Mania Rating Scale (YMRS) is carried out several times by an expert of clinical psychology, unaware of the project, in the following intervals: patients’ first visit, after 2 weeks, after 1 month, after 2 and 3 months.

Young Scale with 11 items developed by Young et al. [15], helps to determine presence or absence of manic symptoms and their severity based on criteria mentioned in Diagnostic Statistical Manual of Mental disorders (1978). Subject is supposed to do an interview in a clinical check which takes between 15-30 minutes.

To answer the questions, subjects are asked to express their feelings about each of the 11 items during the past 48 hours. The psychologist’s observations during the interviews are also included. At the end of each stage, symptoms, medication side effects and the rate of improvement are measured.

RESULTS

Mean age of participants in control and trial group was 38.6±10.3 and 39.2±12.3, respectively. Also, 46.9% of the trial group and 51.7% of the control group were male gender.

The mean score obtained from Young questionnaire decreased from 26.69, at first, to 9.59, after 3 month. The score also decreased for the control group, at the same period, from 21.38 to 16.62 (Fig 1).

As you see, score reduction after 2 weeks in not significant compared to first test in the trial group yet for the rest of the study period it was significant. However, in the control group, the observed reduction was only significant after 3 months. Comparing the reduced scores of both group at all times to the first test at the beginning of the study is indicative of a significant difference which is more outstanding after 3 month in the control group (Table 2, Fig 2).
Table 1: Scores of Young questionnaire in both groups during the study period

<table>
<thead>
<tr>
<th>Time</th>
<th>Trial group (Mean±Sd)</th>
<th>Control group (Mean±Sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the begining</td>
<td>26.69±10.84</td>
<td>21.38±6.39</td>
</tr>
<tr>
<td>2 weeks after</td>
<td>25.41±10.55</td>
<td>20.97±6.31</td>
</tr>
<tr>
<td>1 month after</td>
<td>20.75±8.86</td>
<td>18.83±6.01</td>
</tr>
<tr>
<td>2 months after</td>
<td>15.78±7.35</td>
<td>17.76±5.60</td>
</tr>
<tr>
<td>3 months after</td>
<td>9.59±5.78</td>
<td>16.62±5.29</td>
</tr>
</tbody>
</table>

Table 2: Young score reduction rate comparison between the two groups during the study period

<table>
<thead>
<tr>
<th>Time</th>
<th>Trial group (Mean±Sd)</th>
<th>Control group (Mean±Sd)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the begining</td>
<td>1.28±1.05</td>
<td>0.41±0.63</td>
<td>0.942</td>
</tr>
<tr>
<td>2 weeks after</td>
<td>5.94±3.17</td>
<td>2.55±1.45</td>
<td>0.029</td>
</tr>
<tr>
<td>1 month after</td>
<td>10.91±4.62</td>
<td>3.62±1.50</td>
<td>0.000</td>
</tr>
<tr>
<td>2 months after</td>
<td>17.09±7.69</td>
<td>4.76±2.01</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 3: Comparison of changes in Young scores during the study period with the beginning

<table>
<thead>
<tr>
<th>Time</th>
<th>Trial group (Mean±Sd)</th>
<th>Control group (Mean±Sd)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks after</td>
<td>5.35±4.58</td>
<td>1.91±2.89</td>
<td>0.001</td>
</tr>
<tr>
<td>1 month after</td>
<td>22.51±7.63</td>
<td>12.15±6.14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2 months after</td>
<td>41.60±10.75</td>
<td>17.24±5.50</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3 months after</td>
<td>64.31±15.95</td>
<td>22.43±6.98</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Fig. 1: Changes in scores of Young questionnaire in both groups during the study period

Fig. 2: Young score reduction rate comparison between the two groups during the study period
DISCUSSION AND CONCLUSION

Although depression is commonly attributed to mood disorder caused by deficiency in Folate and B12 [16-21], the present research indicates significant decrease in the scores of Young questionnaire among the trial group. A research carried out in Tunisia (Ezzaher et al.) in which 92 manic patients were tested in terms of homocysteine. They found out that 95% of the patients have high level of homocysteine while indicated suboptimal levels of Folate and B12. Previous findings indicated that supplements like Folate and B12 are very helpful for the improvement of hyperhomocysteinemia patients with mania [10] which is consistent with results obtained in the current research. Dittmann et al. [11] concluded that increasing homocysteine level leaves an adverse effect on verbal learning, delayed memory and manic patients’ performance.

Further research are recommend to measure the items once at the beginning and then periodically during the study. Also, it is better to do the research in a longer follow up period.

REFERENCES


