The efficacy of complementary use of memantine in treatment of schizophrenia with chronic course

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Abstract: Memantine, a drug approved by the FDA for the treatment of moderate to severe Alzheimer's disease, acts as a weak nonselective NMDA receptor antagonist. This study aimed at evaluating the efficacy of complementary use of memantine in treatment of schizophrenia with chronic course. This clinical trial study was conducted on 60 patients with chronic schizophrenia Diagnosis was established using DSM-IV criteria. The antipsychotic medication dose was kept constant for at least six weeks before entry and throughout the entire study period. Memantine was started on day one at a single morning dose of 5 mg, as add-on to antipsychotic drugs. Dose was titrated weekly by 5 mg, up to 20 mg dose at eighths week. Clinical assessments were performed monthly, using the Positive and Negative Syndrome Scale (PANSS). Participants comprised of chronic schizophrenia. Mean age of the study patients was 44.15 ± 9. 65 years. Memantine and adding it to the consumption of other antipsychotic drugs had not any significant effect on Positive and Negative scale. In the total score of PANASS in three levels of evaluation, there was no significant different between two groups which represent that adding memantine to risperidone had not any significant effect on Positive and Negative scale, combination one and general pathology. Memantine add-on to risperidone therapy was not associated with improvement in negative and positive symptoms in refractory schizophrenia patients.

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1. Introduction

Schizophrenia is a mental disorder characterized by a breakdown of thought processes and by a deficit of typical emotional responses. Common symptoms are delusions and disorganized thinking including auditory hallucinations, paranoia, bizarre delusions, disorganized speech, and it is accompanied by significant social or occupational dysfunction.(de et al. 2013; Kishi and Iwata 2013) The onset of symptoms typically occurs in young adulthood, with a global lifetime prevalence of about 0.3–0.7%. Diagnosis is based on observed behavior and the patient's reported experiences. It's not known what causes schizophrenia, but researchers believe that a combination of genetics and environment contributes to development of the disease. (Kotermanski et al. 2013; Rezaei et al. 2013) Problems with certain naturally occurring brain chemicals, including the neurotransmitters dopamine and glutamate, also may contribute to schizophrenia. Neuroimaging studies show differences in the brain structure and central nervous system of people with schizophrenia. While researchers aren't certain about the significance of these changes, they support evidence that schizophrenia is a brain disease.(Uribe et al. 2013; Pae 2013) The primary treatment of schizophrenia is antipsychotic medications, often in combination with psychological and social supports. Hospitalization may occur for severe episodes either voluntarily or involuntarily. Long-term hospitalization is uncommon since deinstitutionalization beginning in the 1950s, although it still occurs.(Sekar et al. 2013; Sani et al. 2012) Community support services including drop-in centers, visits by members of a community mental health team, supported employment and support groups are common. Some evidence indicates that regular exercise has a positive effect on the physical and mental health of those with schizophrenia.(Lee et al. 2012; Pohanka 2012) Phospholipid metabolism occurs in cell membranes and although regional differences are described by Jensen *et al.*, these are not neurotransmitter-specific. This research suggests increased phospholipid metabolism in the anterior cingulate area of people with schizophrenia. Previous studies suggest that this is supportive evidence for a neurodegenerative mechanism in schizophrenia. They also review the effects of neuroleptic and anxiolytic medications on brain phosphorus metabolism.(de et al. 2012; Namba et al. 2011) Memantine is a drug currently licensed for use in people with moderate to severe Alzheimer's dementia. It is a non-competitive, low-affinity *N*-methyl-D-aspartate (NMDA) antagonist. Glutamate-mediated excitotoxicity and/or receptor dysfunction is involved in the pathogenesis of several neuropsychiatric and neurological disorders. Memantine partially blocks these NMDA receptors, preventing a neurotoxic influx of calcium.

Theoretically, it is neuroprotective for glutamate-receiving neurons.(Smith et al. 2011; Chen et al. 2010) The aim of this study was to evaluate the efficacy of complementary use of memantine in treatment of schizophrenia with chronic course.

2. Material and Methods

This clinical trial study was conducted on 60 patients with chronic schizophrenia in Razi hospital, Tabriz from March 2012 to march 2013. This study was approved by ethic committee of Tabriz university of medical sciences. Written consent was obtained from all the patients. Diagnosis was established using DSM-IV criteria. The antipsychotic medication dose was kept constant for at least six weeks before entry and throughout the entire study period. At entry, all participants underwent a psychiatric clinical interview, including medical history and laboratory assessments. Memantine was started on day one at a single morning dose of 5 mg, as add-on to antipsychotic drugs. Dose was titrated weekly by 5 mg, up to 20 mg dose at eighths week. Compliance was monitored by pill counting and by participants' reports. All assessments included a psychiatric evaluation, detailed selfreports of side effects, and the completion of all rating scales. Clinical assessments were performed monthly, using the: Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The study was carried out in an inpatients setting. Patients were closely monitored and assessed daily for adverse events or clinical worsening. Vital signs and blood samples were obtained biweekly for assessment of hematological, blood chemistry and liver and kidney functions values.

Data analysis

SPSS version 16 was used as statistical software. Data analysis was performed according to the intention-to-treat method. Analysis of variance (ANOVA) with repeated measures was used to compare the symptoms at all four time points, followed by Bonferroni post hoc test. The significance level was set at pb.05. A paired t test was used to assess changes before and after treatment. All results are expressed as mean±SD.

3. Results

All participants underwent a 64-section CTA Participants comprised of chronic schizophrenia. Four patients left the study. There were 28 men an 28 women. Age (mean ± SD) of the participants was 44.15 ± 9. 65 years. Participants had been hospitalized for 42.12 ± 24.66 days before beginning study medication and had 6.34±2.12 hospitalizations prior to the current one. Forty seven (83.92%) patients had a history of smoking. Information obtained from the t-test demonstrated no significant difference between the two groups on the first day ($P>0.05$). On twenty-eighth day, G12 scale that indicates a lack of insight and judgment were statistically different between two groups that can represent a significant insight and knowledge in memantine group. But on fifty-sixth day, the activation subscale of the G4, G5, P4 between the two groups were statistically different between two groups ($P<0.05$). Of the activate subscale only G4, G5 that respectively indicating the tension and dominant modes were statistically different between two groups and reflects the high dominant mode and tension and low levels of activation in the intervention group than the control group. In other Positive and Negative Syndrome syptoms, there were no significant different between two groups ($P>0.05$). Memantine and adding it to the consumption of other antipsychotic drugs had not any significant effect on Positive and Negative symptoms. In the total score of PANASS in three levels of evaluation, there was no significant different between two groups which represent that adding memantine to risperidone had not any significant effect on Positive and Negative symptoms, combination one and general pathology.

4. Discussions

The first-line psychiatric treatment for schizophrenia is antipsychotic medication, which can reduce the positive symptoms of psychosis in about 7–14 days. Antipsychotics, however, fail to significantly ameliorate the negative symptoms and cognitive dysfunction. In those on antipsychotics, continued use decreases the risk of relapse. The use of typical and atypical antipsychotics has provided marked improvement for many schizophrenic patients.(Dedeurwaerdere et al. 2011; de et al. 2010) Numerous patients, however, do not achieve full remission of symptoms, often having recurrent episodes. Several adjunctive therapies have been researched targeting the *N*-methyl-D-aspartic acid (NMDA) receptor. With respect to side effects typical antipsychotics are associated with a higher rate of extrapyramidal side effects while atypicals are associated with considerable weight gain, diabetes and risk of metabolic syndrome.(Francis 2009; de et al. 2009) Some atypicals such as quetiapine and risperidone are associated with a higher risk of death compared to the typical antipsychotic perphenazine, while clozapine is associated with the lowest risk of death. It remains unclear whether the newer antipsychotics reduce the chances of developing neuroleptic malignant syndrome, a rare but serious neurological disorder. (van et al. 2009; Gilmour et al. 2009) Our findings in this preliminary study show that memantine, a weak non-competitive NMDA

antagonist, which was used as add-on therapy for patients with schizophrenia with residual symptoms, had low beneficial effects on their mental status but not on their cognitive functioning. Thomas et al. described clinical improvement with addition of memantine to catatonic schizophrenia patients. (Thomas et al. 2005) A case series of three schizophrenia patients treated with memantine add-on showed improvement in BPRS scores.(Gama et al. 2005) The lack of data regarding the effect of memantine on schizophrenia patients could be partially explained by the notion that administrating an NMDA antagonist, such as memantine, potentially could have deleterious effects, as NMDA channel blockers such as MK-801 or PCP induce psychosis, data which led to the notion that schizophrenia neuropathology was linked to hypofunction of the NMDA receptor.(Lieberman et al. 2009; Hugdahl et al. 2007) Our hypothesis that memantine would not worsen the clinical status of patients with schizophrenia was based on data from studies examining the safety of memantine administration to patients with dementia as well as to healthy subjects, and data generated from studies with amantadine which exerts NMDA antagonism combined with dopaminergic activity. In our study, we found that memantine and adding it to the consumption of other antipsychotic drugs had not any significant effect on Positive and Negative symptoms. In the total score of PANASS in three levels of evaluation, there was no significant different between two groups which represent that adding memantine to risperidone had not any significant effect on Positive and Negative symptoms, combination one and general pathology. Several studies with amantadine administered to schizophrenia patients showed no significant worsening effect on mental status. Thus, our findings in this study support the safety of these compounds in schizophrenia patients. Indeed, amantadine and memantine differentially affect striatal dopaminergic transmission, which could indicate that these two related aminoadamantanes display distinct pharmacodynamic properties. In contrast to our study, Rands et al. demonstrated that memantine would appear to be a suitable candidate as a neuroprotective agent for people with schizophrenia, based on its NMDA-receptor-blocking properties. This drug is currently in use as a treatment for people with moderate to severe Alzheimer's dementia. (Rands 2005)

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