Original Article

Efficacy of Memantine as Adjunct Therapy for Autism Spectrum Disorder in Children Aged <14 Years

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Abstract

Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a recent increase in prevalence. A timely appropriate treatment for the disorder may play a crucial role in improvements in behaviors, interactions, and communications in an individual's life. It appears that evaluation of therapeutic approaches to the patients is essential and of importance. Thus, the aim of this study was to evaluate the efficacy of memantine as adjunct therapy in children with ASD. **Materials and Methods:** This randomized single-blind clinical trial included 60 children with ASD aged <14. The children undergoing applied behavior analysis (ABA) were divided into two groups of placebo and memantine (5 mg/day: a half of tablet in the morning and a half in the evening). After a 3-month course, improvements in symptoms of ASD were evaluated in both groups based on Gilliam autism rating scale. The collected data were analyzed with SPSS (version 20) using independent samples *t*-test, paired samples *t*-test, Chi-squared test and Fisher's exact test. **Results:** Both groups were similar in baseline characteristics including age, gender, and ASD symptoms ($P > 0.05$) but post intervention, total scores of ASD symptoms in both groups of memantine (mean $score_1 = 95.20 \pm 14.49$; mean $score_2 = 73.50 \pm 9.81$) and control group (mean $score_{before} = 91.50 \pm 14.35$; mean $score_{after} = 89.63 \pm 13.95$) showed a decrease which was only significant in intervention group ($P < 0.001$). **Conclusion:** Accordingly, memantine administration as adjunct therapy can be more effective in improvement of ASD symptoms in children than ABA alone. Thus, it can be considered as a new selective adjunct therapy.

Keywords: *Autism spectrum disorder, children, memantine*

Introduction

Autism spectrum disorder (ASD) refers to a pervasive developmental disorder with severe impairment of social interaction and communicational skills as well as manifestations of stereotyped behaviors, interests, and activities.[1-3] In this children, problems in emotional behaviors, motor skills particularly using the hand for delicate works, routine daily activities, plays, learning language, and natural speech as well as issues in imitation of others.[4,5]

The prevalence of ASD among 5-year-old children is 6.26/10,000 in Iran versus 116.1/10,000 in England.[6,7]

The most common presentations of ASD are difficulties in social communication, traits, and routines. To clinically diagnose ASD, Diagnostic and Statistical Manual of Mental Disorders (DSM) has provided observed behavior criteria.[1] Despite the determinant role of genetic and environmental agents, the main cause of ASD is still unknown.[8] Although difficulties in spoken language acquisition are experienced by many, the most recent DSM editions have ignored this key feature by which ASD may be identified.[1]

Therefore, given difficulties existing in three sections of social communication and repetitive stereotyped behaviors among ASD; nowadays, they are known as the most important criteria for autism diagnosis.[1]

Taking into account these symptoms, early diagnosis of the disease can be so important to timely treat the children and to improve their life quality. Due to the increased hope of improvement in the medical condition of the children undergoing effective therapy, it is never too late to start treatment. The children can be potentially more successful than others to acquire educational skills, to learn painting, playing music, doing

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mathematical calculations and so on. A common therapy for ASD is applied behavior analysis (ABA).[1-3] The recent studies have suggested a multidimensional efficacy of behavioral therapies based on ABA in children with autism but using adjunct therapies it can enhance this improvement.[4]

In spite of the existence of medications for dealing with hyperactivity and irritability in children with ASD, a reliable improvement in key features of ASD which has not been reported.

Recently, some studies have reported that the treatment of social deficits in children with ASD using glutamatergic agents is not only safe but also effective. ASD is usually accompanied with glutamate (Glu) dysregulation. The increased activity of Glu has been proved by neuroimaging studies as well.[9-11]

There is modest evidence of using Glu-modulating agents including amantadine, lamotrigine, and D-cycloserine for treatments of key ASD symptoms.[12-14] In this respect, a noncompetitive receptor antagonist for N-methyl-D-aspartate with moderate-affinity is memantine hydrochloride. Memantine can be administered as adjunct therapy for psychiatric disorders including attention deficit hyperactivity disorder (ADHD), bipolar disorder, and obsessive-compulsive disorder.[15] The improvements in ADHD symptoms as well as executive dysfunction of adults with ADHD have been pointed out in open-label treatments using memantine.[16,17] Treatments for ASD using memantine are restricted to children and adolescents except of a single pediatric study with a small number of adults.[4] The acceptable improvements in attention, language, social interaction, irritability, hyperactivity and repetitive behaviors have been suggested in these studies.[18-20]

Therefore, given the progressive prevalence of ASD and the necessity of proper early treatment for children with ASD to improve their behavior and social interaction as well as their verbal and nonverbal communications, it seems that the exploration of new therapeutic approaches is of great importance. On the other hand, there are limited national studies in the field, so to discover medications with less complications, the current study aims to evaluate the efficacy of memantine as adjunct therapy for the common approach to children with ASD based on Gilliam autism rating scale (GARS).

Materials and Methods

This randomized, double-blind trial included children with ASD presenting at child psychiatric clinic of Noor and Hazrat-e-Ali Asghar hospital in Isfahan from March 2016 to March 2017. The sample size of 30 children in each group was estimated based on a confidence level of 95%, a statistical power of the test of 80%, standard deviation equal 20 and between these two groups a minimum difference of 15 (expected value). Sixty children enrolled in the study using convenience sampling. The participants were children aged <14 years, with an ASD diagnosed by the child psychiatrist and using GARS and without any other major pediatric disorders including ADHD, mood disorder, ankyloglossia, and so on. In addition, children with any disease which can be affected by memantine and leads to worsening the condition or children with kidney disease were excluded from the study. The patients who showed sensitivity to the memantine would be out of study (no case was found in this regard).

This study was approved by local ethics committee (Isfahan University of Medical Sciences, Iran; Ethical code: IR.MUI.REC.1396.683) and written informed consent was obtained from all patients. In addition, if the participant or their parents were not willing to cooperate or to complete the treatment, the participant would be excluded but fortunately no case was excluded, and sample size did not change [Figure 1].

Initially, the parents were justified by the leading resident (the researcher) and a psychologist and following obtaining informed written consent from their parents. Children were assessed using GARS questionnaire, and calculation of their scores classified into four subscales (including stereotyped behaviors, verbal/nonverbal communication, social interaction, and growth disorders) was included in the study.

It should be noted that questionnaires were filled out by mothers of children at the clinic.

GARS test has been based on the definitions provided by the American autism association (1994) and American psychiatric association and with rely on DSM-IV. GARS test is appropriate for individuals aged 3–22 years and can be filled out by parents and experts at school/home. GARS is composed of four subscales (including stereotyped behaviors, verbal/nonverbal communication, social interaction and growth disorders), each consists of 14 items. These items are scored as follows: 1 = Never observed; 2 = Sometimes observed; 3 = frequently observed. At the level of micro scale, the growth disorders' items are evaluated by Yes/No based on what was stated by the parents or who was caring the child during first 36 months of child's life.[21]

Then, the children were allocated randomly divided into two groups of control group (administered treatment using behavioral training based on ABA + previous common medications + placebo [Prepared by faculty of pharmacy in Isfahan University of Medical Sciences]) and intervention group (administered treatment using behavioral training based on ABA + previous common medications + memantine [Osvah Pharmaceutical Co., Tehran, Iran]) through randomized block design (15 blocks with size of 4 to compose two group of 30). In addition to registering the baseline scores of GARS test, demographic

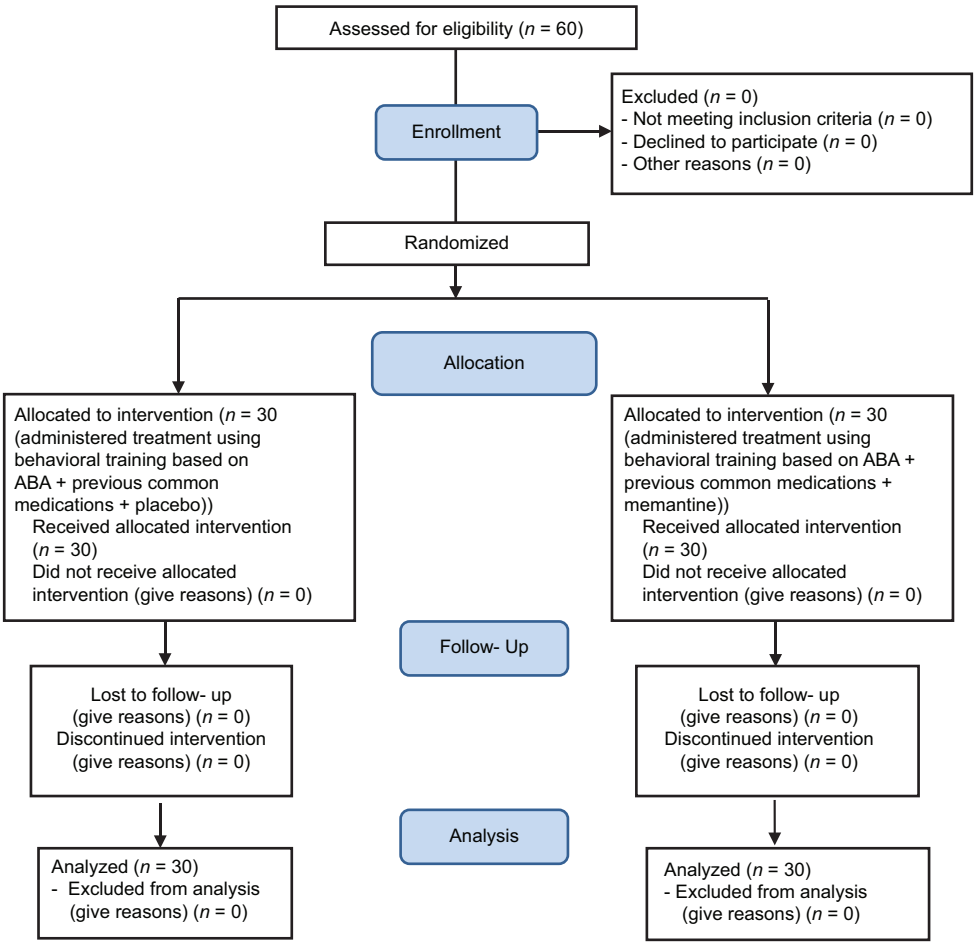

Figure 1: Consort flow diagram

information such as age, gender, occupation, and education of the parents, were recorded.

Training based on ABA principles was performed for all children by an experienced psychologist. The most important stages in behavioral training were focused on taking apart the disability as a great common problem into separated controllable behavioral units and assigning these behaviors to various manipulative environments.

For the intervention group, the oral tablet of memantine (5 mg/day; half in the morning and a half in the evening) was administered. It should be noted that if the treatment did not lead to expected improvement (decrease in the score of GARS), the dosage of medication could be increased weekly to reach the maximal dose of 20 mg/day. Fortunately, the current study did not require these measures. The placebo was administered for controls, instead of memantine.

Both drugs (memantine and placebo) were the same in appearance, shape, color, and odor and encoded with A and B, thus, the patients were blinded to the intervention.

The course of the intervention lasted 3 months, and ongoing behavioral trainings as well as taken drugs were checked out by the researcher.

After the completion of the intervention course, the scores of children's disorders were reassessed using the questionnaire.

Finally, the collected data were analyzed with SPSS software version 20 (SPSS, Inc., Chicago, IL, USA). Given the normality of data distribution (using Kolmogorov–Smirnov test), parametric tests (including independent samples *t*-test, paired samples *t*-test, Chi-squared test, and Fisher's exact test) were applied. For all analyses, a significance level of <0.05 was considered statistically significant.

Results

The current study included 30 children with ASD as the control group (male = 24 [80%], female = 6 [20%]; mean age = 9.50 ± 3.86y) and 30 children with ASD as the intervention group (male = 22 [73.3%], female = 8 [26.7%]; mean age = 10.07 ± 3.48) ($P > 0.05$). The mean age of mothers and fathers of controls group were 40.73 ± 6.19 and 38.03 ± 6.96 years versus 41.89 ± 7.61 and 38.39 ± 7.20 years in the intervention group ($P > 0.05$). There was no association between underlying variables and the assignment of patients to groups of intervention and control [Table 1].

On the other hand, evaluation of ASD symptoms by GARS questionnaire indicated that there is no significant difference between growth disorders in control group (mean score = 8.07 ± 2.15) and in intervention group (mean score = 7.89 ± 2.08) (P = 0.758). In addition, baseline stereotyped behaviors, communications, and social interactions were similar in both groups (P > 0.05); but post intervention, symptoms of stereotyped behaviors, and social interactions significantly decreased in both groups (P < 0.001) while only communication in intervention group showed decrease. Moreover, GARS's total score significantly decreased in intervention group post intervention (mean score = 95.20 ± 14.49) compared to preintervention (mean score = 73.50 ± 9.81), while this reduction was insignificant in control group (preintervention mean score = 91.50 ± 14.35 vs. post intervention mean score = 89.63 ± 13.95; P = 0.057) [Table 2].

Table 1: Demographic characteristics of children, fathers, and mothers in both groups

Characteristics	Intervention group (n=30)	Control group (n=30)	P
Child sex, n (%)			
Male	22 (73.3)	24 (80)	0.761
Female	8 (26.7)	6 (20)	
Child age, year	10.07±3.48	9.50±3.86	0.553
Number of children, n (%)			
1	21 (70.0)	24 (80)	
2	3 (10)	2 (6.7)	0.709
3	4 (13.3)	4 (13.3)	
4	2 (6.7)	0	
Mother characteristics			
Age, year	41.89±7.61	40.73±6.19	0.847
Occupation, n (%)			
Housewife	23 (76.7)	24 (80)	0.983
Employee	7 (23.3)	6 (20)	
Education, n (%)			
≤ diploma	24 (80)	18 (60)	0.311
Associate degree	2 (6.7)	4 (13.3)	
Bachelor	4 (13.3)	8 (26.7)	
Prenatal problems	4 (13.3)	5 (16.7)	0.718
Childbirth, n (%)			
Natural	9 (30)	11 (36.7)	0.580
Cesarean	21 (70)	19 (63.3)	
History of mental disease, n (%)	4 (13.3)	2 (6.7)	0.415
History of physical disease, n (%)	5 (16.7)	6 (20)	0.578
Father characteristics			
Age, year	38.39±7.20	38.03±6.96	0.526
Occupation, n (%)			
Unemployed	7 (23.3)	5 (16.7)	0.536
Employee	7 (23.3)	10 (33.3)	
Self-employed	14 (46.7)	10 (33.3)	
Other	2 (6.7)	5 (16.7)	
Education, n (%)			
≤ diploma	20 (66.7)	18 (60)	
Associate degree	4 (13.3)	5 (16.7)	0.959
Bachelor	6 (20)	7 (23.3)	
History of mental disease, n (%)	4 (13.3)	3 (10)	0.999
History of physical disease, n (%)	3 (10)	2 (6.7)	0.999

Ultimately, the evaluation of the effects of confounders (such as the age of children, fathers and mothers, the gender of child, and so on) on variations in scores of stereotyped behaviors, communications and social interactions using covariance test suggested that with adjustment of these agents, changes in total score, and scores of stereotyped behaviors and social interactions is still significantly greater in case group (21.700, 11.033 and 9.966, respectively) than control group (1.866, 0.99, and 0.500, respectively) (P < 0.001). However, there was still no significant difference between variations in communications scores of children in both groups (P = 0.769) [Figure 2].

Discussion

Autistic disorders are identified as medical conditions can be experienced in early childhood and last forever, without any known treatment so far and easily reversible. Although the leading cause is unclear, both genetic and environmental agents can be involved. According to a newly stated theory, neuromigrational development may be affected by neuroglial cells can cause neuroinflammation leading early brain alterations in autistics.[22] The role of Glu in early stages of brain growth is obvious while neuroprotection, neuronal development, and learning may be influenced by NMDA receptor modulation. Hence, it appears that memantine may be involved in. Previously, the study of treatment for smaller sample size of autistics using memantine indicated positive effect of the medication on language.[18]

In this respect, the single-blinded controlled clinical trial attempted to assess the efficacy of memantine as adjunct

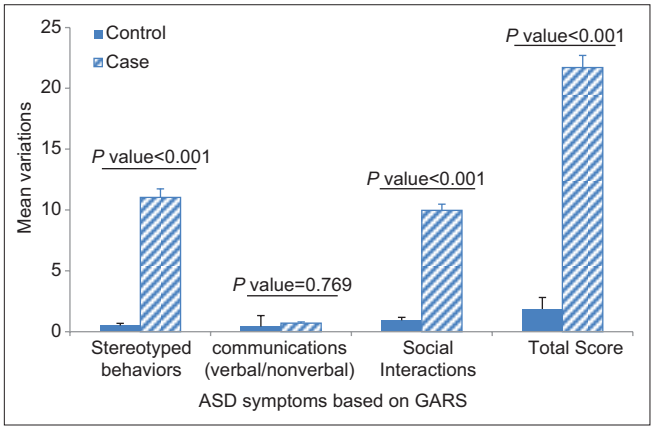

Figure 2: Calculation and comparison of variations in scores of autism spectrum disorder symptoms between two Groups (With adjustment of cofounders [covariate] such as age and gender of children, and basic characteristics of their fathers and mothers)

Table 2: Calculation and comparison of mean scores of autism spectrum disorder symptoms between two groups pre- and post-intervention

Variables	Intervention group (*n*=30)	Control group (*n*=30)	*P***
Growth disorders	7.89±2.08	8.07±2.15	0.758
Stereotyped behaviors			
Before	29.93±6.46	27.87±9.03	0.312
After	18.90±3.68	27.37±8.58	<0.001
*P**	<0.001	0.016	
Communications (verbal/nonverbal)			
Before	31.63±6.88	31.50±6.36	0.938
After	30.93±6.78	31.07±6.02	0.936
*P**	<0.001	0.633	
Social interactions			
Before	33.63±4.52	32.13±8.03	0.337
After	23.67±2.66	31.20±8.02	<0.001
*P**	<0.001	0.001	
Total score			
Before	95.20±14.49	91.50±14.35	0.325
After	73.50±9.81	89.63±13.95	<0.001
*P**	<0.001	0.057	

*Significant level of comparison after vs. before intervention in each groups **Significant level of comparison between two groups

treatment for children aged <14 years. Not only the participants were similar in age and sex but also their fathers and mothers were also similar in demographic characteristics such as age, mental disease, and physical disease (like hypertension and hyperlipidemia), prenatal problems, number of children, and so on. The similarity of these factors can be considered as the strength of the study to comparison of these two groups because the incidence of autism can be affected by environmental agents such as viral infections in mothers, taking valproic acid and thalidomide during pregnancy, hypothyroxinemia in mother during pregnancy,[22,23] metabolic conditions of mother during pregnancy for example diabetes, obesity, the age of parents, and pregnancies intervals.[24] Therefore, no significant difference between two groups regarding these factors can be useful for acquiring more reliable citable findings.

The evaluation of the efficacy of memantine as adjunct therapy for ASD common treatment based on ASD symptoms provided in GARS questionnaire indicated that initially, both groups were similar in three dimensions of stereotyped behaviors, communication, and social interactions. However, after treatment (within three months), the group of children receiving memantine showed a significant decrease in these three dimensions while another group using common treatment showed a reduction only in two dimensions of stereotyped behaviors and social interactions. Although verbal communication was improved considerably, overall the improvements of verbal/nonverbal communication were not significant statistically. Despite no significant difference between the two groups in demographic characteristics of the children and their parents, the adjustment of these factors as confounders and reanalysis of the results suggested no significant role of the factors in the improvements in both groups.

In line with the current study, many studies have reported the effectiveness of the common treatment (using training-based approaches like ABA). For example, Peters-Scheffer *et al*. meta-analysis included 344 children with ASD. As shown their results, the ABA approach can strongly influence the variables of nonverbal intelligence, spoken/conceptual language, and stereotyped behaviors as well.[25]

Ahmadi *et al*. study evaluating the effectiveness of ABA approach as the intervention in general symptoms of ASD, stereotyped behaviors, communicational difficulties, social interactions, cognitive concepts, mathematics, self-assistant, and verbal skills during consecutive 5 years on 20 children and adolescents with ASD; showed that there is a significant difference between each year and baseline year in all above-mentioned attributes pre- and post-intervention.[26]

Indeed, ABA approach can be as the basic intervention applied as the treatment for individuals with developmental disabilities especially ASD.[27] In addition to this intervention, there are other interventions to reduce autistic difficulties including social and communicational problems. The trainings of social skills for autistic children includes various techniques such as group interventions, social stories, social problem-solving, and medication-based interventions.[28,29]

The result of ABA approach used for controls in our study was in agreement with studies above and many other studies. However, the main aim of our study was evaluation of the efficacy of memantine as adjunct treatment for the routine approach, and as shown the results, it showed greater and significant improvement than control group.

In line with our study, the results of many literatures indicate efficacy of the medication in enhancement of social behavior, concentration, language, eye contact, and learning.[4,18,30-32]

Another study evaluating the efficacy of memantine on children and adults with idiopathic autistic disorder and incubatory growth disorder based on Clinical Global Impressions – Improvement Subscale (CG-I); found a significant improvement in 23% of cases and a moderate improvement in 47% of cases and the maximum improvement was observed in language and social behaviors as well.[19]

Aman *et al*. evaluating the safety and efficacy of memantine in autistic children, found that based on Social Responsiveness Scale, no significant difference between

groups in the primary efficacy outcome of caregiver/parent ratings, was observed; however, it was improved at week 12 in both groups compared to preintervention.[33]

Although the results of abovementioned study were in agreement with our study, what distinguishes the studies is that our study evaluated the condition of children immediately after a 3-months' course of intervention (memantine as adjunct treatment) in comparison with the baseline but that study benefits from a 12-week to 48-week follow-up postintervention.

Furthermore, although all studies mentioned here are in agreement with the current study regarding the effectiveness of memantine in social interactions, communication, and repetitive and stereotyped behaviors of the children, the scales of calculation and evaluation of the improvement differ and mostly CG-I was applied. In fact, using GARS as the indicator of ASD symptoms alone can be pointed out as a limitation of our study. GARS just measures the reduction in the symptoms on behavioral skills; however, it is not useful to measure developments in increased intelligence, enhanced knowledge, understanding the meanings and more advanced concepts. Thus, further studies are suggested to evaluate other characteristics of the children such as intelligence, learning difficulties, and so on.

Conclusion

As shown the results, memantine as adjunct treatment can lead to improvements of autistic children's conditions and reduction in ASD symptoms including stereotyped behaviors, communication, and social interactions based on GARS.

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Conflicts of interest

There are no conflicts of interest.

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