

Study of the effect of Memantine therapy on the treatment of dyslexia in children

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Background: Reading disorder (RD) is one of the important complaints in children with learning disorders (LD) that is prevalent in 4% of children in the United States. Treating this disorder includes education of reading practices and treating psychological disorders, and there are no exact medications prescribed in these children. Memantine has been effective in treating memory problems in Alzheimer Dementia, obsessive-compulsive disorder, autism disorder, and other psychological diseases. The aim of this study is to evaluate the effect of memantine in improving RD in children. **Materials and Methods:** In this randomized clinical trial, 62 children, with RD in Pediatric Psychiatry Clinics of Noor and Ali-Asghar Hospital in Isfahan from 2015 to 2016, were participated. They were randomly assigned to two groups of equal number, one receiving education plus memantine and the other education plus placebo. RD was evaluated at the beginning, 1 and 3 months after intervention by Iranian standard reading and dyslexia test (Nama). **Results:** Mean (standard deviation) age of participants was 7.55 (0.60) years. Most of the participants were boy (55%), most having parents in 36–45-year-old age group (52% and 48% for fathers and mothers, respectively), and also most parents in diploma and bachelor educational group (61% and 60% for fathers and mothers, respectively). There were statistical significant difference in trend of total score ($P = 0.034$), word chain ($P < 0.001$), rhyming ($P < 0.001$), text comprehension ($P < 0.001$), and letter fluency ($P = 0.002$), subscale between two groups. However, the difference of time trend between two groups was not significant in word reading ($P = 0.14$), word comprehension ($P = 0.06$), phoneme deletion ($P = 0.12$), reading nonwords ($P = 0.32$), and category fluency ($P = 0.06$). **Conclusion:** Adding memantine to educational practices is effective in improving RD in school-age children with LD.

Key words: Dyslexia, learning disorder, memantine

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INTRODUCTION

Learning disorder (LD) is one of the disorders in children who have disturbances in growth and developmental processes including perception and comprehension, speech, and written language that may manifest itself in hearing, verbal expression, reading, writing, and mathematical aspects.^[1] This definition does not include children with disability, mental retardation, emotional, environmental, economic, and cultural deprivation. On the other hand, these children have normal intelligence quotient, but they are less than their peers in educational aspects.^[2] LD includes disorders in reading, writing, or mathematics.^[3]

Reading disorder (RD) is a specific developmental disorder with symptoms that can be persistent until adulthoods. About 4%–5% of children and adolescents experienced this disorder around the world.^[4] Reading ability is very important in life and learning this ability takes times like the other abilities, and it should be considered as one of the important goals of education in children because having reading ability is essential for learning school and nonschool subjects.^[5] Although children with RD have normal intelligence, they usually did not experience satisfactory academic progress or continued their education with difficulties or dropped out which had negative economic, social, cultural, emotional, and mental effects on children and society.^[6]

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Treating RD includes explaining disorder for RD children's parents and teachers and justifying them. Treatment duration depends on the severity of disorder and psychological symptoms. RD therapy has two parts as followed: education of reading and spelling out practices and treating accompanied psychological disorders.^[5] Studies demonstrated that pharmacological treatment is not considered for RD and it is useful just when other psychiatric disease such as attention deficit hyperactivity disorder (ADHD) is present and treating this psychiatric disease can improve reading disabilities remarkably.^[5] There are several studies suggested that using methylphenidate (Ritalin) improves RDs, but it cannot be considered as a complete treatment for this disease.^[7] Other studies evaluated meclizine as an antinotion sickness medication in RD children, but it has not significant effects, and there are limited case reports with positive effects of this drug special in children with both RD and ADHD.^[8] According to other evaluation, Piracetam was effective in improving RD in children.^[9]

Memantine is widely used in treating Alzheimer disease and sometimes prescribed in autism and obsessive-compulsive disorder (OCD) patients.^[10] This drug is a nonselective antagonist of N-methyl-D-aspartate (NMDA) receptor and modulates glutamate activity as a neurotransmitter involving in memory and learning. In normal situation, glutamate attached to NMDA receptor and allows calcium to enter the cell. Supra-activation of these receptors causes excessive calcium entering to neuronal cells which leads to nerve cell deaths and may result Alzheimer dementia. Memantine inhibits these processes partially and protects cells. This drug well tolerated by patients without any psychotic side effects.^[10-12] Studies showed the efficacy of this drug in treating children with pervasive developmental disorders and ADHD and improving eye contact, repetitive actions, attention, and language.^[13]

There are some issues about RD such as: high costs of employing private teacher for affected children, lack of exact pharmacological treatment for this disorder and need for finding a drug as a treatment with low side effects. Therefore, this hypothesis was raised that Due to the efficacy of memantine in some psychiatric disorders, whether this drug is useful in treating RD or not? The aim of this study is to evaluate the effects of memantine in treating RD children.

METHODS

In this randomized clinical trial study, 62 children with RD who referred to Pediatric Psychiatry and psychology Clinics in Noor and Ali-Asghar Hospital in Isfahan from 2015 to 2016, were participated [Figure 1]. The inclusion criteria were as followed: age <14 years; documented diagnosis for

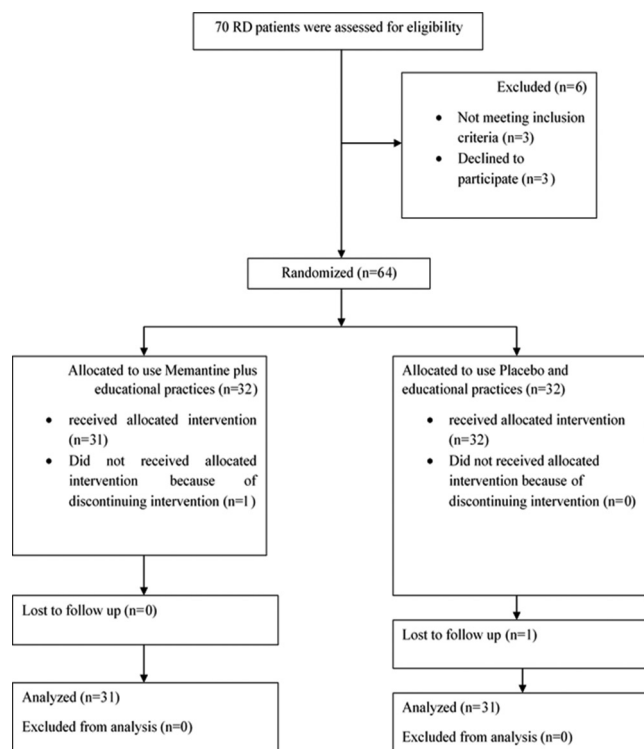


Figure 1: Consort diagram about the stage of trial designation and sampling

RD using Iranian standard reading test (Nama);^[14,15] lack of any psychiatric disorders such as ADHD, stuttering or other; intelligence quotient above of 85 according to Wechsler Intelligence Scale-Revised for children, done for children just before intervention;^[14] lack of any disease that has interaction with using memantine; and parent's willingness to participated their children in this study. Exclusion criteria include having any underlying disease; presenting side effects due to using memantine; and unwillingness of parents to participate their children in this study in every time of the study. Inclusion and exclusion criteria were evaluated by the pediatric psychiatrist.

Considering the confidence level and power equal 0.95 and 0.80, respectively, the required sample size was determined 32 participants per each group. However, regarding the possibility of loss of participants, seventy RD patients were assessed for eligibility at first; during the study, three patients excluded because not meeting inclusion criteria and 3 of them declined to participate, then from 64 residual patients, one participant from each group was excluded because of one patient not received allocated intervention and unwillingness of one's parent to following the study [Figure 1].

This study was explained for children's parents and consent forms were completed.

At the beginning, demographic data were collected by interviewing with parents and then, an Iranian standard

reading and dyslexia test. Nama test in Iranian language comes from abbreviation of the family names of inventors who design it^[14] was done for all participants to evaluate their reading skill.

This test aims to evaluate school child ability in reading and diagnose children with dyslexia. This test is a collection of ten subtests in three scopes including reading, perception and comprehension, and phonological awareness.

These ten subtests are as followed: word reading, word chains, rhyming, picture naming, text comprehension, word comprehension, phenomenon deletion, reading nonwords, letter fluency, and category fluency, described as below.

Word reading subtest includes three category (high frequency, moderate frequency, and low frequency words) each category includes forty words and triable must read and pronunciation them in 2 min, the score is determined by the number of correct read words, and the minimum score of this subtest is 0 and the maximum of it is 120.

Word chain subtest includes of some word chains, in each chain, there is three or four meaningful words and triable must separate meaningful words using pencil in 2 min, score is determined by the number of separated words.

Rhyming subtest includes twenty words, for each word, three words are suggested as same rhyme, but one of them is correct, the limited time for this subtest is 2 min, and the minimum score is 0 and maximum is 20.

Picture naming subtest includes two cards, each card exhibits twenty pictures and triable must naming the pictures of each card in 1 min, the minimum score is 0, and the maximum is 40.

Text comprehension subtest includes three texts which include three stories, triable must listen to the stories and then answer the questions about the story, the score is determined by the numbers of correct answers, and the range of score is 0–22.

Word comprehension subtest includes thirty words with a question about meaning, definition, or utility of each word score is determined by the number of correct answers and it's range is 0–30.

Phoneme deletion subtest includes thirty words, triable must read each words in 2 min after deletion of a word's phoneme which examiner determines it, for example, says umber after deletion lea in umbrella, and score range is 0–30.

Reading nonword subtest includes forty meaningless words and triable must read them correctly in 2 min, score range is 0–40.

Letter fluency subtest includes three letters they display for triable, and he/she must say the words begin with this letter in 3 min, the score is determined by the number of words triable says.

Category fluency subtest includes six categories: name of girls, name of boys, name of body organs, name of fruits, name of colors, and name of cookery instruments, triable must say words about each category, score is determined with the numbers of words triable says. Total score results from summation of ten subtests.

The validity of this Iranian test was evaluated and Cronbach's alpha of word reading subtest was 0.98 and in dual coding attitude was 0.97.

Cronbach's alpha of rhyming subtest in sextet coding attitude and dual coding attitude was 0.93 and 0.66, respectively; Cronbach's alpha of picture naming subtest (it has two forms of A and B) in A form and in tetramerous and dual coding attitude was 0.927 and 0.860, respectively, and in form B in tetramerous and dual coding attitude was 0.970 and 0.901, respectively. Cronbach's alpha of word comprehension subtest in sextet and dual coding was 0.723 and 0.871, respectively. Cronbach's alpha of phoneme deletion subtest in tetramerous and dual coding was 0.963 and 0.961, respectively. Cronbach's alpha of reading nonwords subtest in tetramerous and dual coding was 0.983 and 0.980.^[14] After doing this test, all participants (62) were randomly assigned into two groups with the equal number using random block allocation. In the first group (intervention group), educational practices were provided and also memantine was prescribed (initial dosage was 0.25 mg/kg twice daily for 1 week, and if it was tolerated, the dosage further was titrated 5 mg weekly upward to a maximum dosage of 20 mg twice daily, the mean dosage administered to intervention group is 10.82 mg). This treatment was continued for 3 months because effects of this intervention have been proved after 12 weeks in one study, some of side effects have been detected in this group are headache, dizziness, and constipation.^[16,17] In the second group (nonintervention group), educational practice similar to the first group was provided and they were prescribed for placebo that has similar shape, size, and color to memantine tablets, and a number of placebo tablets prescribed in nonintervention group was equal with a number of memantine tablets prescribed in intervention group. These medications were provided by Abidi pharmacological company and Pharmacy Department of Iran University of Medical Sciences (IUMS) for this study. One and three

months after starting intervention, all participants in both groups were done reading and dyslexia tests again, and the score of each subtest was recorded separately. If each patient showed any side effects of using memantine or placebo, they treated and then excluded from the study.

Educational program contains ten sessions as followed: in the first session, psychologist evaluated education prerequisites including memory, and attention; in the second session, psychologist improved children's visual and auditory memory and trained two syllable words; in the third session, visual and auditory memory, frosting test, and learning two syllable words were practiced and training three syllable words was beginning; in the fourth session, practices were done for improving attention abilities and learning three-syllable words and training four syllable words was started; in the fifth session, practices for improving accuracy were done and word making is completely practiced by making two, three, and four syllable words; in the sixth session, frosting practices were done and training two-part word was beginning; in the seventh session, sequence memory and fluent reading were practiced; in the eighth session, sequence memory, fluent reading, recognition, and comprehension were practiced; in the ninth session, visual accuracy, recognition, fluent reading, and comprehension were practiced; and in the tenth session, all these practices were reviewed. This educational program was held one session in a week. These education sessions were done for each child separate to other children and pediatric psychologist practiced with children in private sessions.^[18,19]

Data were collected in special forms for each participant and then analyzed by Statistical Package for the Social Sciences version 20 (SPSS corp, Chicago, IL, USA). For reporting variables, we used mean (standard deviation [SD]) and frequency (percent) for qualitative and qualitative variables, respectively. Time trend of the two groups was compared applying repeated-measure ANOVA test. A two-sided α level of 0.05 was used to assess statistical significance.^[20] This study was approved by Regional Bioethics Committee of IUMS (IR.MUI.REC.1394.3.538) and it has been registered in IRCT (IRCT2016091329807N1).

RESULTS

At first, age, parents' age, and educational level among all the participants and also the two groups were evaluated. Mean (SD) age of participants was 7.55 (0.60) years. Most of the participants were boy (55%), having parents in 36–45-year-old age group (52% and 48% for fathers and mothers, respectively), and also parents in diploma and bachelor educational group (61% and 60% for fathers and mothers, respectively). Age, mother age, father age, mother

educational level, and father educational level groups were not significantly different between two groups ($P = 0.915$, 0.61 , 0.493 , 0.62 , and 0.695 , respectively) [Table 1].

The between groups analysis to compare differences in trend of change of the total scale and all the subscales between two groups showed that there was statistically significant difference in trend of total score ($P = 0.034$), word chain ($P < 0.001$), rhyming ($P < 0.001$), text comprehension ($P < 0.001$), and letter fluency ($P = 0.002$) subscales; however, this difference was not significant in word reading ($P = 0.14$), picture naming ($P = 0.06$), word comprehension ($P = 0.12$), phoneme deletion ($P = 0.32$), reading nonwords ($P = 0.52$), and category fluency ($P = 0.06$) subscales [Table 2].

The within-group analysis to compare differences during the study process for all the subscales separately for each group showed that, in intervention group except reading nonwords ($P = 0.20$) for all the subscales, there were significant changes over the study period ($P < 0.05$). In nonintervention group except reading nonwords ($P = 0.075$) and category fluency ($P = 0.09$), all the subscales were significantly changed during the study time period ($P < 0.05$) [Table 2].

The pairwise comparison to test differences between the measurements showed that, in intervention group, the

Table 1: Comparison of baseline characteristics in memantine and placebo groups

	Intervention, n (%)	Control, n (%)	Total, n (%)	P
Sex				
Male	18 (58)	16 (52)	34 (55)	0.610
Female	13 (42)	15 (48)	28 (45)	
Father age (years)				0.493
25-35	3 (10)	4 (13)	7 (11)	
36-45	15 (48)	17 (55)	32 (52)	
46-55	11 (36)	6 (19)	17 (27)	
56-65	2 (7)	4 (13)	6 (10)	
Mother age (years)				0.620
25-35	2 (7)	4 (13)	6 (10)	
36-45	14 (45)	16 (52)	30 (48)	
46-55	11 (36)	7 (23)	18 (29)	
56-65	4 (13)	4 (13)	8 (13)	
Father degree				0.695
Under diploma	10 (32)	8 (26)	18 (29)	
Diploma and bachelor	19 (61)	19 (61)	38 (61)	
Master	2 (7)	4 (13)	6 (10)	
Mother degree				0.599
Under diploma	6 (19)	8 (26)	14 (23)	
Diploma and bachelor	19 (61)	18 (26)	37 (60)	
Master	6 (19)	5 (16)	11 (18)	
Child age				0.915
Mean (SD)	7.56 (0.59)	7.55 (0.60)	7.55 (0.60)	

SD = Standard deviation

Table 2: The mean score of subscales in reading and dyslexia test at the beginning, 1 and 3 months after intervention

Subtests	Group	Mean (SD)			P* (within group)	F (1,60)	P** (between group)
		Pretest	1 month after	3 months after			
Total score	Intervention	724.19 (21.82)	810.19 (19.72)	807.00 (28.91)	<0.001 ^c	4.7	0.034 ^c
	Control	715.90 (25.23)	799.16 (26.18)	800.65 (25.52)	<0.001 ^c		
Word reading	Intervention	82.22 (1.59)	93.32 (1.43)	95.41 (6.16)	<0.001 ^c	2.2	0.146
	Control	80.48 (1.34)	90.16 (1.38)	94.51 (1.32)	<0.001 ^c		
Word chain	Intervention	75.91 (1.13)	88.45 (2.00)	87.12 (2.24)	<0.001 ^c	15.7	<0.001 ^c
	Control	73.64 (1.28)	78.64 (1.77)	79.96 (1.56)	0.013 ^c		
Rhyming	Intervention	98.35 (1.06)	106.48 (0.96)	105.29 (1.50)	0.005 ^c	14.6	<0.001 ^c
	Control	92.03 (2.41)	101.51 (0.80)	97.83 (2.82)	<0.001 ^c		
Picture naming	Intervention	54.87 (0.75)	62.16 (0.62)	61.80 (0.72)	<0.001 ^c	3.6	0.064
	Control	56.58 (0.70)	64.12 (0.990)	62.35 (1.02)	<0.001 ^c		
Text comprehension	Intervention	46.80 (1.10)	52.32 (1.33)	53.16 (1.20)	<0.001 ^c	37.9	<0.001 ^c
	Control	49.90 (0.97)	62.03 (1.78)	64.67 (1.23)	<0.001 ^c		
Word comprehension	Intervention	63.83 (1.14)	71.77 (1.41)	69.58 (1.99)	0.001 ^c	2.2	0.128
	Control	61.87 (0.08)	75.19 (1.86)	74.06 (1.54)	<0.001 ^c		
Phoneme deletion	Intervention	67.22 (0.70)	76.4 (0.56)	74.83 (1.09)	<0.001 ^c	1.0	0.325
	Control	66.33 (0.82)	75.45 (0.86)	73.87 (1.33)	<0.001 ^c		
Reading nonwords	Intervention	58.29 (0.94)	60.61 (0.91)	61.03 (1.43)	0.200	0.4	0.525
	Control	60.48 (1.30)	62.45 (1.28)	59.06 (1.07)	0.075		
Letter fluency	Intervention	84.33 (0.60)	100.19 (1.77)	100.61 (1.29)	<0.001 ^c	10.7	0.002 ^c
	Control	81.51 (2.04)	94.06 (1.37)	97.29 (1.10)	<0.001 ^c		
Category fluency	Intervention	93.06 (1.24)	98.87 (1.17)	100.74 (1.25)	<0.001 ^c	3.5	0.066
	Control	93.06 (1.62)	95.51 (1.69)	97.00 (0.86)	0.090		

*P for within group analysis (comparing the beginning, one and three months after intervention in each group), **P for between groups analyses (comparing trend of changes during the study between groups), ^c: Statistically significant. SD = Standard deviation

total score and all the subscales at before intervention were significantly different from 1 to 3 months after intervention ($P < 0.01$) except text comprehension at before intervention was not significantly different from 3 months after intervention ($P = 0.18$). However, there was no significant difference between 1 month after intervention and 3 months after intervention.

The pairwise comparison to test differences between the measurements showed that, in control group, the total score and all the subscales at beginning of the study were significantly different from 1 and 3 months after the study ($P < 0.01$) except reading nonwords at the beginning of the study was not significantly different from 1 month and 3 months after the study ($P = 0.223$ and $P = 0.412$) and rhyming at the beginning of the study was not significantly different from 3 months after the study ($P = 0.09$). In control group in some domains such as reading nonwords ($P = 0.002$), letter fluency ($P = 0.01$), and word reading ($P = 0.009$), significant difference was seen between measurements of mean score in 1 month after education and 3 months after the education; however, in other domains, this difference was not significant.

DISCUSSION

Generally, this study showed that using memantine along with educational practices is more effective than

using educational methods alone and in this study comparing mean score changes between intervention and no intervention groups showed that this changing was more in children who received memantine, significantly in total score of reading and dyslexia test and the scores of word chain, rhyming, text comprehension, and letter fluency subtests.

Memantine is a medication approved by Food and Drug Administration in 2003 which has usage in treating Alzheimer patients due to its effects on memory.^[21] This drug is a nonselective NMDA receptor and modulates glutamate activity as memory and learning neurotransmitter. Glutamate is a main motivated neurotransmitter in brain that activates postsynaptic receptors such as NMDA receptors which has a specific role in memory and learning processes.^[10,11] One of neuropsychological features which is important in reading skill progression is working memory. Working memory is a vital ability for primary recognition of reading and then reading perception. Studies showed that children with RDs have poorer functions in neuropsychological tests including immediate memory, memory for names, face memory, and working memory compared to children without RD.^[22,23] In children with dyslexia, poor performance or dysfunction of memory for saving data about phonological structure of language causes problems in reading.^[24] In addition, these children have problems for reminding data that maybe is due to failures in function of short-term memory.^[25]

According to discussion above the role of memory impairment in reading disorder is obvious. On the other hand the effect of memantine in improving memory has been proved, So one can conclude that efficacy of memantine in improving RD is due to the effect of this drug in improving children's memory.

In our study, mean score in the majority of subtests in intervention groups during the time of study increased significantly and there was just one subtest (reading non-words) which did not show any significant changes. In this subtest, the mean score was increased during the study, but this increase was not statistically remarkable. In nonintervention group, the mean score of most subtest showed significant changes during the study except reading nonwords and category fluency subtests. These findings demonstrated that educational practices with or without using memantine have significant effects in improving reading skills in different aspects in children.

In three domains of nonintervention group, the score of 1 and 3 months after intervention was statistically different, but in intervention group, there was no significant difference between 1 month after intervention and 3 months after intervention, this can suggest that using memantine can be speedier in treating process, and in nonintervention group after 3 months, significant result was acquired, and in intervention group after 1 month, significant result was acquired.

About educational and psychological treatments, there are several studies that showed psychological intervention can improve reading functions in children with RDs.^[14] There are other studies which assessed educational practices in treating RDs and demonstrated that the best way is to employ a private teacher to practice reading abilities with children based on asking question by teacher and self-asking question strategies.^[26] In addition, using educational techniques for improving reading skills in school-age children who are at risk for RD can remarkably decrease the incidence of RD.^[27] Interventions based on reading fluency may have positive effects in RD children in improving reading skills,^[28] but according to our knowledge despite all of the studies mentioned above, there is not any study that demonstrated the effects of any drug on children's reading skills.

RD is a combination of disabilities and problems that affected learning processes in several aspects and accompanied with problems in processing speed, short-term memory, visual, auditory, and speech perception and sequences, and motor skills.^[29] There are limited studies that evaluated the effects of education and medication on all domains of reading and dyslexia. Similar studies evaluated some parts of these abilities, but the Nama test which was used in this study evaluated all aspects of disabilities mentioned above.

Children with RD have inadequacy in selective attention, and they have small attention span and visuospatial and phonemic defects.^[30-32] One study in 14 children with pervasive developmental disorder using memantine showed improvement in 28% of children with most effects in memory aspects and improvement in eye contact, visual processing, and increasing focuses.^[13] In other studies, memantine has been useful in OCD patients.^[33,34] Hence, other studies in children have evaluated the effect of memantine on other psychiatric disorders.

One of the limitations of this study is its small sample size, and for further researches, a greater and universal sample size is needed. In addition, in this research, the effects of memantine were evaluated when it is added to educational practices and for assessing the exact effects of this drug and its mechanism it is better to evaluate its effects in improving reading problems separately.

CONCLUSION

Adding memantine to educational practices is effective in improving RD in school-age children with LD.

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Conflicts of interest

There are no conflicts of interest.

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