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The Effect of Memantine on Cognitive Impairments in Patients with Brain Tumour under Radiotherapy: A Randomized Clinical Trial Study

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Abstract

Background: Cognitive impairment is one of the common problems in patients undergoing radiotherapy, but there is no way to prevent it until this time. The aim of this study was to determine the effect of memantine on the prevention of cognitive impairment in patients with brain tumour undergoing radiotherapy.

Method: In this clinical trial study, 70 patients under radiotherapy were selected and randomly divided into two groups. The first group received 10 mg of memantine tablets daily for six month and the second group received placebo at the same dose and time. Cognitive impairment was evaluated through Mini-Mental Status Examination questionnaire and compared between the two groups.

Results: The mean score of cognitive impairment before and after radiotherapy in the control and intervention groups were 27.97 ± 1.52 and 27.66 ± 1.35 (P = 0.26), in the following month were 27.74 ± 1.74 and 27.63 ± 1.35 (P = 0.73), in the following three months were 23.17 ± 1.81 and 24.77 ± 1.44 (P <0.001), and in the following six months were 20.66 ± 1.8 and 23.17 ± 1.42 (P < 0.001). In addition, changes in cognitive impairment score were significantly different between the two groups (P < 0.001).

Conclusion: It seems that memantine is effective in preventing the cognitive impairment in patients undergoing radiotherapy following brain tumour surgery and the implementation of this referee can be associated with improved cognitive function over time.

Keywords: Radiotherapy, Brain, Tumour, Cognitive impairments, Memantine

Introduction

Cognitive impairment is one of the most important side effects of radiation therapy. Studies show that radiation therapy has widespread side effects, the most important of which is the change in neural network and long-term cognitive impairment. In a corneal-cerebral thickness study, 54 patients with brain tumours before and after radiotherapy were investigated using MRI. Results revealed that radiotherapy could change the brain's network topology and decrease the thickness of the cortex. The study also illustrated that brain cortical reduction is much faster than Alzheimer's due to radiotherapy. On the other hand, it causes the separation of different parts of the brain, the coordinated function of which is essential for memory and information recall.[1-4]

Cognitive impairment is a series of disorders and neurological diseases that can be directly or indirectly (sustained or transient) disturbing the cognitive function of the nervous system, causing disturbances in one's awareness of oneself and the surrounding world and abnormalities, and creating certain behavioural abnormalities that greatly affect the individual and social life of the patient. Decreased mental function in this disease may include memory problems, changes in behaviour, difficulty in understanding the language, and difficulty in performing daily activities.[5] Although there has not yet been a method for the prevention and treatment of cognitive impairment due to radiotherapy, in some studies, the use of medications, such as memantine and donepezil, has been effective.[6]

Memantine is a drug of Alzheimer's disease,[5] which has a positive effect on the understanding, mood, and behaviour of moderate to severe Alzheimer's patients.[7] Recent research has demonstrated promising results from the treatment of various patients with memantine. Among the diseases that are thought to be affectively treated by memantine, there is are obsessive-compulsive disorder,[8] anxiety disorders, such as general anxiety disorder,[9] hyperactivity-attention deficit,[10] and coping with cognitive impairment.[11]

Numerous studies have investigated the effects of memantine on cognitive impairment so far and have presented various results in delaying cognitive impairment.[12-14] Therefore, according to the results of various studies, it seems that this drug can help prevent cognitive impairment in patients with a brain tumour that undergo radiotherapy. On the other hand, since a native study has not been done so far in this regard, the present work was conducted to determine the effect of memantine on the prevention of neurological disorders in patients with brain tumours under radiotherapy.

Materials and Methods

This is a double-blind clinical trial study performed in Isfahan, Seyed al-Shohada Hospital in 2018. The target population was patients with brain tumours that underwent radiotherapy at this hospital.

The inclusion criteria were patients with brain tumour, cognitive impairment score greater than 20 before the start of radiotherapy, candidate for radiotherapy, no history of cognitive neurological disorders and patient’s consent to participate in the study. Additionally, the withdrawal of the patient to continue to attend the study for various reasons, the incidence of drug allergy to memantine, and patient's death before the end of the study were considered as exclusion criteria. The Medical Ethics Committee of Isfahan University of Medical Sciences approved this study (ethics code: IR.MUI.MED.REC.1397.320).

The required sample size was calculated to be 35 individuals in each group using the formula for estimating the sample size for comparing the two means and taking into account the 95% confidence level, the 80% power, the standard deviation of the cognitive impairment score obtained in other studies by about 1.2[8], and the least

significant difference between the two groups which was considered as 0.8.

The patients were randomly allocated in two groups using Random Allocation Software (RAS). In this software, the total sample size (70) and the number of groups are entered into the software. The software output contains a list that randomly distributes numbers 1 to 70 in groups A and B. The patients were divided into two groups according to the time of referral according to the list until the sample size reached 35 patients in each group.

The method of doing this was that after obtaining permission from the Medical Ethics Committee of the Isfahan University of Medical sciences (code: IR.MUI.MED.REC.1397.320), 70 patients were selected to participate in the study and distributed randomly in two groups of 35 individuals. The first patient was assigned to one of the two intervention or control groups and the subsequent patients were randomly assigned one and the other, respectively, to the time of referral in the two groups, making the sample size was sufficient in each group.

In the next stage, all the patients were examined for cognitive impairment via Mini-Mental Status Examination **(**MMSE) questionnaire at the time of entering the study and their demographic characteristics were recorded in a data collection form. The Persian version of the MMSE questionnaire has good validity and reliability according to the study of Seyedian et al. and the Cronbach's alpha coefficient for the Persian version was 0.81.[15]

At the next stage, the patients underwent radiotherapy and from the first day of radiation therapy, the patients received daily 5 mg of memantine tablets (produced by the Sobhan Pharmaceutical Company, Iran) for 12 hours apart after meals for six months. In the second group, the patients were given placebo tablets containing starch made by Sobhan Pharmaceutical Company at the same dose and time and after the end of six months, the MMSE questionnaire was completed again by the patients. The total dose of radiation in the patients between 30-60 Gy and daily dose of 2-3 Gy was five days a week.

MMSE is a questionnaire for measuring the Mini-Mental Status Examination. This tool is used to assess the quality of consciousness in dementia. MMSE is a paper-based test with a maximum score of 30, with lower scores indicating more severe cognitive problems. This test consists of three questions with five points, five questions with one point, three questions with three points, one question with two points and four questions with one point. Its five-point items include: time orientation, place orientation, and serial sever. Its three-point items include: execution of a three-step command (get up, walk, and sit), recent memory, and instant memory. A two-point item is a name for two objects, each object containing one point. Its one-point items also include read, write, repeat, and shape.[16]

The cognitive actions that are evaluated in this test are: 1- orientation, 2- registration, 3-attention, calculation, 4- recent memory, 5- evaluation of various linguistic functions, 6- spatial thinking. Thus, individuals with a score above 25 were evaluated as without disturbances, and those with a score of 25 to 20 with a probability of degradation, and a score of less than 20 with definitive cognitive degradation according to standardized questionnaires.[16]

Isfahan University of Medical Sciences supported the present study and we registered the design in the research faculty of medical school of Isfahan with the code of 395112.

Radiation therapy was performed in all the patients with 6 MV photon. Moreover, using patients' records and asking patients' companions, other information, including the duration of illness, type of tumour, tumour location, and frequency of radiotherapy, were determined and recorded. Data were collected and analysed through SPSS software version 23 via t-test,

Chi-square, and ANOVA with repeated observation tests at a significant level of $P < 0.05$.

Results

In this study, 70 patients underwent radiation therapy in two groups of 35, intervention and control groups. During the treatment, no diseases were detected due to unwanted complications or other exclusion criteria. The two groups did not have a significant difference in duration of illness, age, sex, type of tumour, and tumour site (Table 1).

The mean dose of received radiation in the control and intervention groups respectively was 50.09 ± 11.38 and 45.03 ± 12.2 and there were no significant differences between the two groups ($P = 0.08$).

Radiation was measured in 31 patients (12 from the placebo group and 19 from the memantine group) in the whole brain, in 30 (18 from the placebo group and 12 from the memantine group) in the total lesion, and in five (three from the placebo group and two patients from the memantine group) in total lesion with a 2-cm margin and four patients (two from each group) had a total lesion with a margin of 3 cm and the location of radiation in two groups was not significantly different ($P = 0.4$). The mean dose of DVH (Dose volume histogram) was not statistically significant between the two groups ($P = 0.14$).

The mean scores of cognitive impairment before and after intervention respectively were 27.97 ± 1.52 and 27.66 ± 1.35 mg / dl ($P = 0.26$) in the control and intervention groups In the following one, three, and six months, they were 27.74 ± 1.42, 27.63 ± 1.35 ($P = 0.73$), 23.17 ± 1.81 and 24.77 ± 1.44 ($P < 0.001$), and 20.66 ± 1.8 and 23.17 ± 1.42 ($P < 0.001$), respectively. The patients receiving memantine at three months and six months had a lower cognitive impairment than the placebo group (Table 3).

In-group changes with ANOVA with repeated observations showed that the change in cognitive impairment score was significant in both groups ($P < 0.001$), but the reduction in memantine recipient group was significantly lower ($P = 0.008$). In Figure 1, the trend of cognitive impairment during the intervention period is depicted in two groups.

Compared to the results before the treatment, there was no cognitive dysfunction, but in one month after the start of treatment, three patients of the control group and three of the intervention group (8.6% of each group) were probably diagnosed with cognitive impairment ($P < 0.99$) and in the following three months after treatment, 19 patients in the control group and four in the intervention group (54.3% versus 11.4%) were likely to have cognitive impairment ($P < 0.001$). Six months after the initiation of the treatment, 33 of the control and 20 of the intervention group (94.3% versus 57.1%) were likely to have cognitive impairment ($P < 0.001$). It should be noted that according to the MMSE questionnaire during the treatment period, no definitive cognitive impairments were observed in any diseases (Figure 2).

The results demonstrated that there were no significant correlations between received radiation dose and cognitive impairment score, indicating that the correlation coefficient was -0.09 ($P = 0.47$), (-0.02) ($P = 0.90$), and (-0.66) ($P = 0.64$) respectively in the one, three, and six months after the start of the treatment. There were no significant correlations between cognitive impairment score and received radiation dose. The mean radiation dose in the patients with and without cognitive impairment in the before intervention was 47.4 ± 12.3 and 49.7 ± 8.1 grey ($P = 0.66$) and 47.4 ± 12.3 and 49.7 ± 8.1 ($P = 0.66$), 47.3 ±12.2 and 48 ±11.8 ($P = 0.83$), and 44.9 ± 13.1 and 48.4 ± 11.6 ($P = 0.30$) grey respectively in the one-, three-, and six-month follow-ups. In addition, we observed no statistical differences between the patients with and without MMSE.

Evaluation of cognitive impairment in terms of site of radiation exposure did not

show any significant relationships between cognitive impairment score and site of radiation exposure (P = 0.74). There were also no significant differences in cognitive impairment score in terms of site of radiation exposure (P = 0.61).

Table 4 represents the mean and standard deviation of cognitive impairment score in terms of the extent and location of radiation. It should be noted that according to repeated measures ANOVA, other variables including age (P = 0.69), sex (P = 0.95), tumour type (P = 0.91), tumour location (P = 0/26), duration of the disease (P = 0.33), radiation dose (P = 0.55), and site of radiation (P = 0.42) did not significantly affect the changes in cognitive impairment score.

Discussion

The purpose of the current study was to determine the effect of memantine on the prevention of cognitive impairment in patients with brain tumours under radiotherapy. Herein, two groups of 35 patients underwent radiotherapy after brain tumour surgeries and were treated with memantine and placebo. The two groups did not show a significant difference in the distribution of demographic and clinical variables and there were no confounding effects on the factors mentioned in the study. Therefore, the observed differences between the two groups were probably due to the effect of memantine on the prevention of cognitive impairment.

The results of the present paper showed that the administration of six months of memantine had a significant effect on reducing the incidence of cognitive impairment in the patients; hence, at the end of three and six months of treatment, the patients receiving memantine had a lower cognitive impairment than the placebo group. In this regard, the results of Brown et al. revealed that the administration of 24 weeks of memantine in patients undergoing radiotherapy following a brain tumour surgery resulted in a reduction of cognitive impairment in patients undergoing radiotherapy of the brain of 0.78. In this study, the incidence of cognitive impairment in the memantine and placebo groups were 53.8% and 64.9%.[12] In another study by Slade et al. in 2016, the incidence of cognitive impairment was less than 10% in the memantine-recipient group and 56% in the control group and the difference between the two groups was of significance.[13] The results of these studies are similar to ours. In the study by Attia et al. in 2014, the effect of Donepezil and memantine on the prevention of cognitive impairment in patients undergoing radiotherapy was studied and there were no significant differences between the two drugs, but in the patients receiving memantine, the severity of the cognitive impairment was lower.[14]

Another study found that memantin had a positive effect on the prevention of cognitive impairment in the other diseases, such as High-Molecular-Weight Aβ Oligomers,[17] multiple sclerosis,[18] and neuropsychological factors.[19] Dohopolski et al. shed light on the effect of memantin on the decrease of cognitive impairment among patients with brain tumour undergoing radiotherapy.[20]

Memantine is a neuroprotective agent that can be employed for the improvement of cognitive impairments in patients undergoing brain radiotherapy. This drug can also be used for some other neurological complications due to radiotherapy, such as decline in memory, cognitive function, and processing speed.[21]

According to the results of our study, the mean dose prescribed radiation in the intervention group was higher than the control group, but no statistically significant differences between the two groups were seen, which may be on account of the bias in the study. Receiving a higher dose of radiation in the intervention group was a random result because the patients were randomly allocated in the two group considering the inclusion criteria. At the same time, due to the direct relationship between the received radiation dose and the

incidence of cognitive impairment, more studies are needed in this field.

At the same time, having a control group is the strength of the present work, but this study had limitations, such as small sample size and the follow-up period of different doses of radiation was short, which may make it difficult to generalize the results to all patients. Therefore, it is suggested that more studies be carried out in this field.

Conclusion

The results of this study showed that memantine is effective in preventing the incidence and severity of cognitive impairment in patients undergoing radiotherapy following brain tumour surgery since this drug is well tolerated by patients and has very low toxicity. Administration of this referee can, over time, be accompanied by better cognitive function of patients. In other words, administration of memantine increases the incidence of cognitive impairment in patients undergoing radiotherapy.

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Conflict of Interest

None declared.

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Table 1. Demographic characteristics in the patients of the two groups

Variables		Groups		*P*
		Control	Intervention	
Mean of duration of disease (months)		8.3 ± 12.3	6.2 ± 14	0.51
Mean of age (year)		45.5 ± 16.2	46.1 ± 12.8	0.86
Sex	Male	16(45.7)	15(42.9)	0.81
	Female	19(54.3)	20(57.1)	
Kind of tumour	Astrocytoma grade2	10(28.6)	7(20)	0.37
	AML	1(2.9)	0(0)	
	Metastatic	9(25.7)	16(45.7)	
	Menangioma	2(5.7)	1(2.9)	
	GBM	7(20)	6(17.1)	
	Lymphoma	1(2.9)	4(11.4)	
	Oligodendro gelioma	1(2.9)	0(0)	
	Adenoma	2(8.6)	1(2.9)	
	Meduloblastoma	1(2.9)	0(0)	
Location	Temporal	13937.1)	10(28.6)	0.28
	Frontal	2(25.7)	15(42.9)	
	Cerebellum	1(2.9)	40(11.4)	
	Parietal	295.7)	2(5.7)	
	Hypophyses	6(8.6)	1(2.9)	
	Other	7(20)	3(8.6)	

Table 2. Mean dose of received radiation

Variables		Groups		***P***
		Control	Intervention	
Mean of dose of received radiation (grey)		50.09 ± 11.38	45.03 ± 12.2	0.08
Site of radiation	Whole brain	12(34.3)	19(54.3)	0.40
	Total lesion	18(51.4)	12(34.3)	
	Total lesion with a 2-cm margin	3(8.6)	2(5.7)	
	Total lesion with a 3-cm margin	2(5.7)	2(5.7)	
DVH mean of dose (grey)		25.32 ± 5.32	26.11 ± 4.67	0.14

DVH: Dose volume histogram

Table 3. Mean score of cognitive impairment before and after intervention

Time	Groups		*P*
	Control	Intervention	
Before intervention	27.97 ± 1.52	21.66 ± 1.35	0.26
One month later	27.1 ± 4.42	27.63 ± 1.35	0.73
Three months later	25.17 ± 1.81	26.77 ± 1.44	<0.001
Six months later	22.66 ± 1.8	25.17 ± 1.42	<0.001
P^{**}	<0.001	<0.001	0.008^{***}

*mean difference between the two groups (T-test)
**mean difference within group (repeated measures ANOVA)
***mean difference between group (repeated measures ANOVA)

Table 4. Mean and standard deviation of cognitive impairment score in terms of the extent and location of radiation

	Extent and location	1 month	3 months	6 months	P^{*}
Extent	Whole brain	27.87 ± 1.28	26.03 ± 1.74	23.94 ± 2.06	<0.001
	Total lesion	27.1 ± 47.61	25.77 ± 2.03	23.73 ± 2.3	<0.001
	Total lesion with a 2-cm margin	27.6 ± 0.89	26 ± 1.41	24.4 ± 0.89	0.001
	Total lesion with a 3-cm margin	28 ± 0.00	27 ± 0.82	24.5 ± 0.58	<0.001
	P^{**}	0.68	0.64	0.85	0.74^{***}
Location	Temporal	27.8 ± 1.4	25.9 ± 1.8	23.4 ± 1.8	,0.001
	Frontal	27.5 ± 1.3	25.3 ± 1.6	23.3 ± 2.1	<0.001
	Cerebellum	27.2 ± 2.6	25.8 ± 2.7	24.2 ± 3.1	0.01
	Parietal	28.5 ± 1	27 ± 0.8	25.5 ± 1.3	<0.001
	Hypophyses	27 ± 2	25 ± 2.9	23.3 ± 2.5	0.003
	Other	28 ± 0.7	25.6 ± 1.8	23.6 ± 1.8	<0.001
	P^{**}	0.58	0.63	0.4	0.610^{***}

*mean difference between the two groups (T-test)
**mean difference within group (repeated measures ANOVA)
***mean difference between group (repeated measures ANOVA)

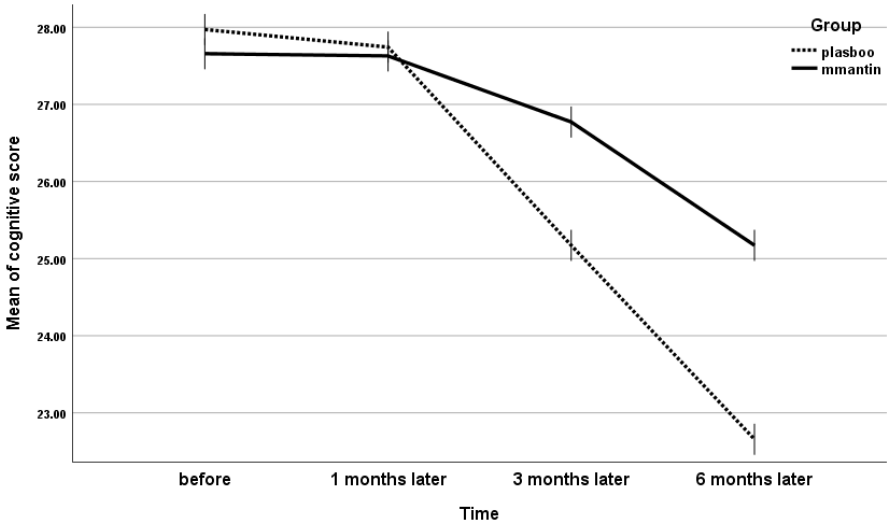

Figure 1. This figure exhibits the mean of cognitive score during intervention.

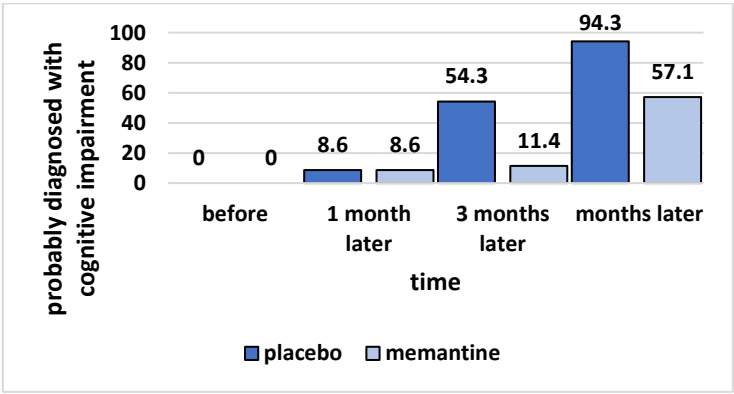

Figure 2. This figure depicts the frequency percentage of cognitive impairment based on MMSE score.