Caspian Journal of Neurological Sciences
http://cjns.gums.ac.ir

Comparing the Effect of Memantine and Placebo on Clinical Outcome of Intracranial Hemorrhage: A Randomized Double Blind Clinical Trial

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 17 July 2015
Accepted: 25 August 2015
Available online: 6 October 2015
CJNS 2015; 1 (3): 11-18

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ABSTRACT

Background: Intracerebral Hemorrhage (ICH) is a stroke type which resulted in disability. Memantine have been supposed to have the effect on the functional status in patients with ICH.
Objectives: Comparing the effect of memantine with placebo on the clinical outcome of ICH.
Materials and Methods: This double-blind clinical trial was conducted in an academic hospital in northern Iran on patients with ICH allocated in memantine and placebo group through the random block method. The patients' neurological status was assessed on admission, the seventh day, upon discharge and ultimately three months after the ICH onset, according to the National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), Barthel Index (BI) and Glasgow Coma Scale (GCS). The data analysis was done by using independent t-test, Chi-square and repeated measure tests in SPSS software version 21.
Results: A total of 64 patients have been allocated into two equal size groups with no significant differences in terms of age or gender (p>0.05). The mean increase in the BI and the decrease in the mRS were significantly greater in the memantine group compared with the placebo group as measured from admission time until three months following the ICH onset (p=0.001 and p=0.049, respectively). No significant differences were observed between the two groups in mortality rate (p=0.492) and the means and changes of the GCS (p=0.331) and the NIHSS score (p=0.211).
Conclusion: Early administration of memantine to ICH patients can result in significant improvement of long-term motor function and functional independence.

Key Words: Memantine; Intracerebral Hemorrhage; Treatment Outcome

➢ ***Please cite this paper as:***
Bakhshayesh-Eghbali B, Hajinnori M, Seyed-Saadat SM, Seyed-Saadat SN, Kazemnezhad-Leili E, Rouhi-Rad M . Comparing the Effect of Memantin and Placebo on Clinical Outcome of Intracranial Hemorrhage: A Randomized Double Blind Clinical Trial. Caspian J Neurol Sci 2015; 1(3):11-18.

Introduction

Stroke is a major cause of mortality and the most common cause of physical disability throughout the world (1,2). In the US, 750,000 cases of stroke occur every year and one fifth of them die (3). Various studies which have been conducted

between 1990 and 2008 in Iran have reported the annual incidence of stroke in different age groups as 23 to 105 per 100,000 persons (4).

Stroke consists of ischemic and hemorrhagic types (3). The hemorrhagic type constitutes only 10% to 20% of the total cases of strokes; however, it has a higher rate of mortality compared to ischemic strokes, and unlike other types of strokes, its mortality rates have not diminished over time (3-9). In the first few hours following a hemorrhagic stroke, the body encounters an excessive release of neurotransmitters (10), also including glutamates, which are the dominant stimulatory neurotransmitter in the brain (11). The accumulation of glutamates in the site of injury and their attachment to the N-Methyl-D-Aspartate receptors is followed by excitotoxic damage, cell dysfunction and ultimately cell death (12). Blocking the glutamate receptors following hemorrhagic stroke may therefore result in a reduced mortality rate and an improved function for the patients (13,14). As a reversible NMDA receptor blocker, memantine was approved in 2003 by the American Food and Drug Administration (FDA) for the treatment of Alzheimer's (15-17). Cochrane's reviews study of three clinical trials on moderate to severe Alzheimer's revealed the positive effects of memantine on patients' cognition, behavior, mood and daily activities (11). Memantine has a good kinetics (12), is clinically well-tolerated and poses no serious side-effects or drug interactions (18).

Studies have shown that memantine can improve cognitive function and reduce the severity of chronic aphasia in stroke patients (19-21). Since the language and motor complications caused by stroke have an immeasurable effect on patients and their families and also impose huge costs on the community's health system (1), the present study was conducted to compare the effects of memantine against placebos on clinical outcomes in patients with intracerebral hemorrhagic stroke.

Materials and Methods

The present randomized, double-blind, clinical trial was conducted as a pilot study from April 2013 to April 2014 in an academic hospital in northern Iran. The research project was registered at www.irct.ir under the No: IRCT201305128490N2 after the approval of the Ethics Committee of Guilan University of Medical Sciences. The study population consisted of patients with supratentorial ICH admitted to the neurology department of hospital and whose diagnosis had been confirmed by a clinical examination and CT scan. Patients entered the study based on the study inclusion criteria, consisting of having an NIHSS score below 20 at the time of entry, having been diagnosed in less than six hours, having had a minimum hospital stay of seven days, being below 80 in age and having a GCS score over five at the time of entry. The study exclusion criteria consisted of having a concurrent ischemic stroke, the use of a pacemaker, having systemic diseases in other organs including liver or kidney failure, severe neuropathies, systemic vascular diseases, severe prior disabilities due to neural or non-neural causes such as orthopedic conditions, a history of previous cerebral hemorrhage, myocardial infarction or stroke, alcohol abuse, cognitive disorder, secondary ICH due to other causes such as brain trauma or cerebral aneurysm rupture, history of using anticoagulants, anti-platelets or non-steroidal anti-inflammatory drugs, pregnancy and intra-ventricular hemorrhage

(IVH). The selected patients after signing the informed consent forms by themselves or their legal responsible were divided through the random block method with a block size of 4 (2:2) into equal groups of 32; one group receiving memantine and the other placebo. Both groups continued to receive their routine treatments and physiotherapy programs on the side. From the day of admission (the first 24 hours following the vascular event), the memantine group first received a 10 mg daily dose of memantine for one month, and if no side-effects presented, the daily dosage was increased to 20 mg for the next two months. The placebo group received the same dose of a placebo over the same period and through the same procedures. Given the lack of studies conducted with similar indices on the effect of memantine on functional outcomes in patients with ICH, the present pilot study was conducted on two groups of 32 patients each. For confirming the randomization, 64 envelops (A and B) were prepared, mixed up and then given to the department nurses. Given the double-blind design of the study, neither the patients nor the neurologist responsible for assessing the patients had any knowledge of the drugs contained in the envelops.

At the time of admission, a questionnaire reviewing the participants demographic details, including their history of using of anticoagulants, anti-platelets and NSAID, history of previous diseases (hypertension, diabetes, ischemic heart disease, *etc.*), history of systolic and diastolic blood pressure and the onset of symptoms prior to hospital admission was filled out for each patients. Medications has been administered by the ward nurse, and the patients' relatives received full instructions on how to administer the medication at the time of the patient's discharge. The study variables were assessed by an expert neurologist with no knowledge of the medication actually being administered or not, who then noted their findings in the questionnaires. Changes to the patients' functional and motor status based on the National Institute of Health Stroke Scale (NIHSS), to their mortality rates following the onset of symptoms, to their functioning and disabilities based on the modified Rankin Scale (mRS), to their daily activities and functional independence based on the Barthel Index (BI) and to their level of consciousness based on the Glasgow Coma Scale (GCS) were measured at the time of admission, on the seventh day, at the time of discharge and three months after the incidence of ICH.

Data were analyzed in SPSS software version 21. The Chi-square test and the independent t-test were used to compare the patients in terms of their age and gender distribution. The independent t-test was used to compare the two groups in terms of their NIHSS, GCS, BI and mRS by time of measuring. The repeated measures test was also used to compare the trend of changes in these indices in studied groups, which were presented in linear plots. $p<0.05$ was considered as the level of significance.

Results

A total of 64 patients divided into two groups of 32 entered the study. The mean age of participants was 67.81±7.4 years in the memantine group and 67.88±7.6 years in the placebo group. In terms of gender distribution, the memantine group consisted of 16 men and 16 women, and the placebo group of 18 men and 14 women. No significant differences were found between the two groups in terms of gender and age ($p>0.05$).

Table 1 presents the NIHSS, GCS, BI and mRS scores obtained at the time of admission, on the seventh day, at the time of discharge and 90 days following the incidence of ICH. According to the table, only the BI score was significantly higher in the memantine group compared to in the placebo group 90 days after the onset of ICH.

Table 1. Scores of NIHSS, GCS, BI and mRS in two groups at different times of the study and comparing between them

Evaluation criteria	Evaluation day	Evaluated group	Number	Mean±SD	*p*-value
NIHSS*	1 day	Memantine	32	5.426±14.19	0.584
		Placebo	32	15.41±3.817	
	7 day	Memantine	32	13.16±5.150	0.264
		Placebo	32	14.81±3.745	
	Discharge day	Memantine	32	12.13±5.123	0.163
		Placebo	32	14.13±3.765	
	90 day	Memantine	32	9.41±4.500	0.132
		Placebo	30	11.33±3.155	
GCS**	1 day	Memantine	32	11.25±1.666	0.706
		Placebo	32	11.59±1.628	
	7 day	Memantine	32	12.69±1.176	0.789
		Placebo	32	12.63±1.238	
	Discharge day	Memantine	32	13.38±0.976	0.694
		Placebo	32	13.22±1.263	
	90 day	Memantine	32	14.81±0.397	0.305
		Placebo	30	14.71±0.466	
BI***	1 day	Memantine	32	59.53±23.327	0.839
		Placebo	32	64.53±9.948	
	7 day	Memantine	32	65.63±18.481	0.870
		Placebo	32	68.13±1.053	
	Discharge day	Memantine	32	69.53±17.103	0.984
		Placebo	32	70.63±10.453	
	90 day	Memantine	32	85.63±12.492	**0.004**
		Placebo	30	78.00±8.158	
mRS****	1 day	Memantine	32	2.94±0.948	0.765
		Placebo	32	2.88±0.942	
	7 day	Memantine	32	2.34±0.745	0.872
		Placebo	32	2.34±0.745	
	Discharge day	Memantine	32	2.19±0.780	0.959
		Placebo	32	2.22±0.792	
	90 day	Memantine	32	1.31±0.693	0.099
		Placebo	32	1.81±1.306	

* National Institutes of Health Stroke Scale, **Glasgow Coma Scale, ***Barthel Index, **** modified Rankin Scale

As shown in table 2, the mean increase in the BI score (p=0.001) and the mean decrease in the MRS score (p=0.049) occurred from the time of admission until three months following the ICH occurrence were significantly greater in the memantine group in comparison with the placebo group. However, no significant difference has been observed between the two groups in their mean scores of the GCS and NIHSS and their mortality rates.

Table 2. The changes of NIHSS, GCS, BI and mRS Scores in two groups at different times of the study

Evaluation criteria	Evaluation day	Evaluated group	Number	Mean±SD	*p-value*
NIHSS*	1 & 7 day	Memantine	32	0.94±1.564	0.161
		Placebo	32	1.28±1.905	
	1 & Discharge day	Memantine	32	1.97±2.117	0.106
		Placebo	32	1.28±1.905	
	1 day & 3 month later	Memantine	32	4.69±2.764	0.211
		Placebo	30	3.83±2.335	
GCS**	1 & 7 day	Memantine	32	-1.44±1.243	0.165
		Placebo	32	-1.03±0.861	
	1 & Discharge day	Memantine	32	-2.13±1.362	0.122
		Placebo	32	-1.63±1.100	
	1 day & 3 month later	Memantine	32	-3.56±1.605	0.331
		Placebo	30	-2.97±1.426	
BI***	1 & 7 day	Memantine	32	-6.09±9.396	0.157
		Placebo	32	-3.59±6.380	
	1 & Discharge day	Memantine	32	-10.00±10.239	0.071
		Placebo	32	-6.09±6.567	
	1 day & 3 month later	Memantine	32	-26.09±20.507	**0.001**
		Placebo	30	-12.50±6.791	
mRS****	1 & 7 day	Memantine	32	0.59±0.615	0.612
		Placebo	32	0.53±0.842	
	1 & Discharge day	Memantine	32	0.75±0.568	0.620
		Placebo	32	0.66±0.787	
	1 day & 3 month later	Memantine	32	1.63±0.707	**0.049**
		Placebo	32	1.06±1.134	

* National Institutes of Health Stroke Scale, **Glasgow Coma Scale, ***Barthel Index, **** modified Rankin Scale

Changes in the indices in the two groups according to the repeated measures test, indicated no significant differences between the two groups in terms of their GCS (p=0.2), mRS (p=0.313) and NIHSS (p=0.582) but a rather significant difference in terms of their BI score has been found (p=0.003) (Diagram 1).

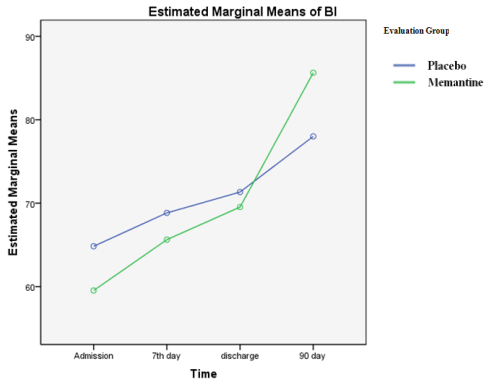

Diagram 1: Comparing the changes course of BI in two groups (p=0.003)

Of the total of 64 patients were examined, the only cases of mortality pertained to two of the patients in the placebo group (3.1%).

Discussion

The present study examined 64 patients divided into two groups which were blindly selected to be prescribed meantine or placebo. The mean increase in the BI score and the mean decrease in the mRS score occurred from the time of admission until three months following the ICH onset were significantly greater in the memantine group compared with the placebo group. In the way that memantine can have a significant role in improving motor function and functional

independence in daily activities in patients with ICH.

Given the public fear of stroke, its outcome has always been questioned by both the patients and their relatives. The medical team should also be able to assess the prognosis and functional outcome of stroke so as to estimate the risk of medical interventions. Several sets of criteria have been designed for determining the functional outcome of stroke including the NIHSS, mRS, GCS and BI (22).

The GCS (Glasgow Coma Scale) assesses and grades the severity of brain damage and scores it based on three functions (limb movements, opening of the eyes and speech), each given scores from 3 to 15. This scale is particularly useful for monitoring changes following head trauma; however, it cannot replace a full neurological assessment (23). The assessment of the patients' level of consciousness based on the GCS score showed improving the level of consciousness over the course of the study in both groups, but no significant differences between the two groups in the mean scores obtained for this variable or the changes to it. In the other words, memantine held no advantage over placebos in the level of consciousness, perhaps showing that memantine has no beneficial effects on consciousness in these patients.

The NIHSS score grades the patients' neurological state based on 14 items (level of consciousness, responding to questions, obeying commands, visual field, facial palsy, horizontal extra- ocular movement, upper and lower limbs motor function, sensation function, ataxia, language, speech, extinction and inattention) which has recently been widely used in different centers and in interventional trials and is scored from 0 to 36 (24). In the present study, no significant differences were observed between the two groups in their mean NIHSS score or the changes to it. The positive effect of memantine on patients' motor functions was previously shown in other studies including a study by Lee *et al*. that observed an improved functional and motor performance in patients with Parkinson's disease following the administration of memantine (25). By studying the effect of memantine on rats, these researchers also noticed a reduced infiltrative inflammation and apoptosis and an induced functional recovery following the incidence of ICH (26). Kafi *et al.* showed that memantine can make significant improvements in neurological function in patients with ischemic stroke (27).

The BI and mRS were used to assess the patients' daily activity and functional independence. The BI assesses 10 items (personal hygiene, bathing, eating, going to the toilet, climbing the stairs, putting on clothes, bowel control, bladder control, mobility and going from the bed to the chair and vice versa) totally scored from 0 to 100, and the mRS assesses 7 items (asymptomatic, no significant disabilities, mild disabilities, moderate disabilities, almost severe disabilities, severe disabilities and death), totally scored from 0 to 6. The mean increase in the BI score and the mean decrease in the mRS score were noticed to be significantly greater in the memantine group compared to in the placebo group from the time of admission until three months following the incidence of ICH, showing a greater functional independence in the memantine group. It should be noted that, although the BI has a strong correlation with the patient’s independence and level of disability, it provides a better description of the patient's

conditions in the case of mild disabilities (28), which may be due to the lack of significant differences, especially at the onset of the disease, when the patient's disabilities must have been more severe. Previous studies have shown that, despite being a safe drug for ALS patients, memantine cannot affect functional disabilities in the short term (29). Prasher argued that memantine can have positive effects on mental disabilities in Alzheimer's patients, just as some other medications including Donepezil, Rivastigmine and Galantamine (30). In the assessment of functional independence, the long-term use of mamantine was found to increase functional independence, which is also consistent with the findings of a study conducted by Luk'ianiuk *et al.*, which showed memantine to improve the mental function as well as the motor function (although to a lesser degree) (21).

Conclusion

The present study showed that the early administration of memantine to ICH patients may result in significant improvement of long-term motor function and also functional independence. Nevertheless, memantine showed no significant advantages over placebo in terms of the effect on the level of consciousness.

Since the present study has not assessed the patients' cognitive problems, future studies are recommended considering this aspect as well and to also use larger sample sizes.

Conflict of Interest

No conflict of interest.

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