ORIGINAL ARTICLE

Therapeutic effect of memantine on patients with posttraumatic headache: A randomized double-blinded clinical trial

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Background: Traumatic brain injury (TBI) can result in different complications. Posttraumatic headache (PTH) is a disabling complication of TBI. We investigated the therapeutic effect of memantine on patients with PTH. **Materials and Methods:** This randomized and double-blinded clinical trial was performed in 2020 in a hospital on 90 patients with head trauma. Patients were divided into two groups. The active group received 5 mg memantine tablet for 2 weeks followed by 10 mg tablet daily for up to 6 months. The control arm received identical placebo tablets. Patients were evaluated at 3 months and 6 months. Headache severity was measured with a Visual Analog Scale for Pain. Headache frequency (per week) and duration were also recorded. **Results:** After 3 months, the patients in the memantine group had significantly lower headache severity (P = 001) and frequency (P = 0.008) in comparison to baseline of the study. However, in the placebo group, there was only significant reduction in the headache duration (P = 0.001), and there was no significant reduction in headache intensity and frequency. After 6 months, there was a significant reduction in headache intensity and duration in both groups (P < 0.05), but only in the memantine group, headache frequency was significantly reduced (P < 0.001). Finally, patients in the memantine group had less headache intensity, frequency, and duration after 6 months of taking memantin than the placebo group.(P < 0.05 for all). **Conclusion:** The administration of memantine for 6 months could significantly lower the severity, duration, and frequency of PTHs.

Key words: Duration, frequency, headache, memantine, severity, traumatic brain injury

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INTRODUCTION

Traumatic brain injury (TBI) has a variety of mechanisms that can result from blunt head trauma, penetrating injury of the skull, rapid acceleration or deceleration of the head, or blast injury.[1] TBI can have short-term and long-term effects on people's health, ranging from symptoms that have a small impact on people's lives to physical, emotional, and psychological disorders that disrupt a person's daily life.[2-7]

Headache is a common manifestation after TBI, especially after mild trauma, with a prevalence rate of 18%–58% in different studies.[8] These headaches can be a manifestation of migraine, tension or other primary causes of headache. According to the International Headache Society,[9] posttraumatic headache (PTH) is caused by sudden movement of the head in the form of acceleration/deceleration and the neck by extension flexion (Whiplash) or due to blunt trauma to the head. In chronic cases, the headache lasts more than 3 months and its severity has not decreased compared to the time of onset.[10]

Experimental treatment for PTH has no reliable history based on clinical trials. There are limited studies on the

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treatment of PTH, most of which have a therapeutic (not preventive) approach. Despite all this, PTH are still not well treated and managed, and self-medication is very common among patients.[11,12]

Memantine is an N-methyl D-aspartate (NMDA) receptor-dependent inhibitor of the glutamate receptor subgroup that is primarily used in the treatment of Alzheimer's disease.[13] Strong animal evidence suggests that during trauma to the brain, significant amounts of glutamate are released and stimulate glutamate receptors.[14,15] In migraine, serum and cerebrospinal fluid (CSF) levels of glutamate rise sharply and play an important role in causing headaches.[16]

One challenge is to target glutamate receptors in the treatment of PTH. Due to its tolerability, early treatment with memantine supplementation after trauma can somewhat alleviate the problem of tolerance. Therefore, in a clinical trial study, we decided to investigate the preventative effect of memantine on acute and chronic PTH. The aim of this study was to answer this question that can early preventative treatments with memantine decrease the frequency, severity, and duration of headaches after TBI and avert the development of chronic PTH or not.

MATERIALS AND METHODS

Study design

This is a randomized and double-blinded clinical trial that was performed in a hospital. The current study was conducted on patients with PTH that referred to our medical center using easy sampling. The study protocol was approved by Research committee of Isfahan University of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR.MUI.MED.REC.1399.124, Iranian Registry of Clinical Trials (IRCT) code: IRCT20201005048944N1). At the beginning of the study, demographic data of patients including age, gender and their past medical history were collected. Patients underwent thorough neurological examinations; the Glasgow Coma Scale was calculated for each patient and data of all primary neurological signs and symptoms and disorders were gathered.

Patients' selection

All patients older than 18 years, referred to our medical center due to head trauma were enrolled in this study. Patients with the lack of proper cooperation, history of any neurologic diseases, history of any psychological diseases, lack of sufficient compliance to the medication, and having any complication following head trauma including infections were excluded. We should note that the diagnosis of the previous migraine and tension headache in patients was determined by exact history taking. Due to the low prevalence of other primary headaches, other headaches were not included in our study.

The diagnosis of PTH was evaluated using the International Classification of Headache Disorders criteria.[9]

Patient classification

Patients were assigned to the treatment and placebo group in double random blocks. In this way, the two patients who entered the emergency and met the inclusion criteria were considered as pairs, and both people who were in a block were randomly assigned to one person in the treatment group and the other person in the control group until the sample size was complete.

For patients in the intervention group, 10 mg of memantine tablets were prescribed daily as 5 mg a tablet for 2 weeks and then 10 mg tablet daily for up to 6 months. The pharmaceutical company of the patients' pills was the same. A placebo was administered to patients in the control group.

Patients were evaluated within 3 months and 6 months by phone calls. The incidence of headache and its severity were evaluated based on the Visual Analog Scale for Pain. Based on this scale, the pain was scored between 10 (most severe pain) and 0 (no pain). The frequency of headache (per week) and durations of headaches were asked and the regarding data were collected.

Statistics analysis

The obtained data were entered into the statistical analyses in this study were performed using IBM SPSS Statistics software, version 24. IBM SPSS Statistics is developed and distributed by IBM Corporation, headquartered at New York, United States. The sample size was calculated based on the ($n = \frac{2(Z_1 + Z_2)^2 S^2}{d^2}$) formula. With this calculation, N was considered to be 45 people for each group.

Quantitative data were reported as mean ± standard deviation and qualitative data as frequency distribution (percentage). Independent *t*-test, Chi-square, and Wilcoxon test were used to analyze the data. $P < 0.05$ was considered a significance threshold. We conducted the Shapiro–Wilk test to assess the normality of the data for parametric variables (duration, severity and frequency of headaches). The results indicated that the data were normally distributed.

RESULTS

During the study, 90 patients were entered into two groups: memantine ($n = 45$) and placebo ($n = 45$). Fourteen patients were excluded from the study due to insufficient

cooperation (n = 8) and drug side effects (n = 6), such as confusion and psychosis. The excluded patients were replaced with other patients based on the inclusion criteria. Initial analysis showed that the study population consisted of 67 males (74.4%) and 23 females (25.6%), with a mean age of 39.96 ± 14.76 years. By assessing the TBI severity, we observed that 68 patients (75.6%) had mild TBI, and 22 (24.4%) had moderate-to-severe TBI. Forty-nine patients (54.4%) had migraine-type headaches and 41 cases (45.6%) had tension-type headaches. There were no significant differences between the two groups of patients regarding gender (P = 0.809), age (P = 0.784), the severity of trauma (P > 0.99), and type of headaches (P = 0.525). These data are indicated in Table 1.

Comparing to the beginning of the study, we observed that patients in the memantine group had significantly decreased headache severity after 3 months (P = 0.001) and both groups had significant improvements in headache severity after 6 months (P = 0.004 for placebo and P < 0.001 for memantine). The duration of headache also improved significantly after 3 months in placebo group (P = 0.001) and in both groups after 6 months (P < 0.001 for placebo and P = 0.002 for memantine group). Furthermore, we observed that the frequency of headaches improved significantly in memantine group after 3 months (P = 0.008) and after 6 months (P < 0.001). Comparing of two groups after 6 months, the memantine group had less headache severity (P = 0.013), less headache duration (P = 0.001), and less headache frequency (P = 0.001) than the placebo group [Table 2].

We also observed that the acute PTH progressed to the chronic headache in 35 patients in the memantine group (77.7%) and 41 patients in the control group (91.1%). However, there were no significant differences between two groups regarding this issue (P = 0.08). Of the 35 patients in the memantine group, 9 cases (25.7%) had severe traumatic injury and 26 patients had mild trauma (74.3%). On the other hand, of the 41 cases in the control group, 9 patients (21.9%) had severe head trauma, and 17 patients (78.1%) had mild traumatic injuries. There were also no significant differences between groups regarding the types of headaches (P = 0.165). These data are shown in Table 3.

Table 1: Analysis of demographic data between two groups

	Placebo	Memantine	Total	*P*
Age (year)	40.85±15.39*	40.13±14.19	39.96±14.76	0.784[a]
Sex				
Male	34 (75.6)	33 (73.3)	67 (74.4)	0.809[b]
Female	11 (24.4)	12 (26.7)	23 (25.6)	
Trauma severity				
Moderate to severe	11 (24.4)	11 (24.4)	22 (24.4)	>0.99[b]
Mild	34 (75.6)	34 (75.6)	68 (75.6)	
Type				
Tension	19 (42.2)	22 (48.9)	41 (45.6)	0.525[b]
Migraine	26 (57.8)	23 (51.1)	49 (54.4)	
Total population	45 (50)	45 (50)	90 (100)	

*Data is represented by mean±SD or *n* (%) and significance level for all tests is considered *P*<0.05; [a]Independent samples *t*-test; [b]Chi-square test. SD=Standard deviation

DISCUSSION

PTHs are known as major problems in injured patients with high prevalence among young adults. This problem could seriously reduce the quality of life in patients and most cases require medical support. Unfortunately, there has not been a definite treatment strategy for this issue. Here, we evaluated the use of memantine in 90 patients divided into two groups. Based on our results, patients that received memantine had significantly lower severity, duration, and frequency of headaches compared to placebo and these reductions could be detected after 3 and 6 months after treatments. These data show the effectiveness of memantine as a therapeutic agent for posttraumatic headaches. However, on the other hand, we observed that memantine had no significant effects on the prevention of chronic headaches.

Previously, various studies have been conducted on the use of memantine for the treatments of different types of headaches. Most of these studies have reported

Table 2: Comparison of severity, duration, and frequency of headaches in both groups

Group	Before treatment	After 3 months	After 6 months	*P* value 1*	*P* value 2*	*P* value 3*
Severity (VAS)						
Placebo	6.13±2.39	6.15±2.41	5.30±2.14	0.224	0.004	0.013
Memantine	6.52±1.07	5.27±2.29	4.37±2.44	0.001	<0.001	
Time (h)						
Placebo	4.71±2.78	3.14±1.18	3.77±1.16	0.001	<0.001	0.001
Memantine	3.61±2.75	4.75±3.91	2.01±2.05	0.325	0.002	
Frequency (per week)						
Placebo	6.33±3.09	6.60±3.12	6.43±3.71	0.765	0.190	<0.001
Memantine	5.74±2.18	5.84±3.66	4.26±2.66	0.008	<0.001	

Data is represented by mean±SD and significance level for all tests is considered *P*<0.05; **P* value 1: Within group repeated measurements (before treatment - after 3 months); *P* value 2: Within group repeated measurements (before treatment - after 6 months); *P* value 3: Between group (placebo vs. memantine) repeated measurements after 6 months. SD=Standard deviation; VAS=Visual Analog Scale

Table 3: Evaluation of acute or chronic headaches based on the groups of patients and type of headaches

	Acute, *n* (%)	Chronic, *n* (%)	*P*
Group			
Placebo	4 (8.9)	41 (91.1)	0.081
Memantine	10 (22.2)	35 (77.8)	
Type of headache			
Tension	4 (28.6)	37 (48.7)	0.165
Migraine	10 (71.4)	39 (51.3)	

acceptable results, especially among patients with migraine headaches, but some other reports have investigated these effects in patients with posttraumatic headaches. In 2018, Kamins and Charles conducted a study on posttraumatic headaches and declared that memantine could have significant improving effects in patients with posttraumatic headaches and is also generally tolerated drug but it has not yet been approved.[8] In another study in 2021, it was reported that tricyclic antidepressants, Serotonin–norepinephrine reuptake inhibitors, candesartan, botulinum, metoclopramide, and diphenhydramine could have significant effects on patients with posttraumatic headaches, but the use of memantine might be associated with better treatment results and lower rates of side effects.[17] The results of our study also support the use of memantine as a therapeutic option in patients with posttraumatic headaches. We observed that the severity, duration, and frequencies of headaches decreased significantly over 3- and 6-months usage of memantine.

In another study by Khan *et al*. in 2021, they investigated the various effects of memantine in patients with TBI. They showed that memantine could be safely used in patients and could control the headaches, but the exact neuroprotective properties of memantine and its effects on cognitive improvements should be further investigated.[18] Other studies have reported the use of memantine in different types of headaches. In 2019, Shanmugam *et al*. evaluated the use of memantine in 60 patients with chronic migraine. They showed that memantine is effective, well tolerated, and safe for patients with migraines, and patients treated with memantine had significantly lower headache frequency after 6 months.[19] In a systematic review in 2021, Mistry *et al*. showed that memantine could be used as a treatment option for episodic migraine, and the treated patients had significant improvements in the number of migraine days and headache severity.[20] These data were consistent with the findings of our study emphasizing the effectiveness of memantine on headache.

Furthermore, studies have reported the beneficial effects of memantine for prophylaxis of episodic migraine[21,22] and it has been explained that these effects are mediated through inhibiting the NMDA receptors.[23] The exact mechanism of effect of memantine on hedaches is not clear. Glutamate is a primary excitatory neurotransmitter in the central nervous system. Strong animal evidence suggests that during trauma to the brain, significant amounts of glutamate are released and stimulate glutamate receptors.[14,15] In migraine, serum and CSF levels of glutamate rise sharply and play an important role in causing headaches.[16]

The main point of our study was that we assessed the effects of memantine on posttraumatic headaches and its different aspects such as severity, frequency, and duration and as shown, only few studies have investigated the use of memantine on posttraumatic headaches. The limitations of our study were restricted study population and performing a single-centered study. We recommend that further multi-centrist evaluation on larger populations should be conducted.

CONCLUSION

Administration of memantine for 6 months could significantly lower the severity, duration, and frequency of posttraumatic headaches. These effects have been investigated in limited studies that reported similar results. We recommend that neurologists should pay more attention to the properties of memantine in this regard.

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Conflicts of interest
There are no conflicts of interest.

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