Original Article

Role of Memantine in Treatment of Migraine

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Objective: To look for the response of the Memantine for migraine in our society.
Methods: This was a prospective observational trial conducted at Neurology department, Services Hospital Lahore over a period of 1 year, from January 2019 to December 2019. A total of 55 patients were included in the study and they were observed for 1) Headache frequency per month; 2) Headache severity as per pain rating scale (1-10 as mild to most severe); 3) Level of distress as per distress rating scale (1-10, as mild to most sever distress); and hindrance of activity of daily living as per Migraine Disability Assessment Scale (MIDAS). These study variables were noted before the start of treatment. Memantine was started to all of the patients and after 3 months of treatment all patients were re-evaluated for same variable. Also side effects of the drug were noted in the study.
Results: The mean age of the patients in our study was calculated as 43±11.42 years. The headache frequency of the patients per month significantly reduced after 2 months treatment. Also in 76.3% of patients, more than 50% reduction in the frequency of headache was noted after the treatment. The mean MIDAS score before start of the treatment was 81.8±14.76. After 3 months of treatment with Memantine, the MIDAS score found was 15.52±2.84 (P value = <0.05). It was also found that minimal side effects of the drug were encountered by the patients in our study.
Conclusions: On the basis of this study, we conclude that Memantine is a safe drug and can be used for migraine management. However still further randomized trials with larger sample size are being recommended.
Keywords: migraine, memantine, midas score.

Introduction

Following anxiety, migraine is the second most common brain disorder. According to a report by World Health Organization, migraine is ranked as 19th disease among all diseases causing disability.[1] Migraine is generally considered as severely disabling disease which reduces significantly the quality of life of the patients. However, inspite of its high prevalence, only 48% of the people know about their diagnosis of migraine and even smaller percentages of patients seek medical advice for it.[2] According to Bukhari FA, majority of patients of migraine in Pakistan do not seek medical advice, rather they get help from local healers and herbal medicine.[3] A neurologist is usually consulted by most of the doctors only when it is of highest severity and is most disabling to their daily routine life. Migraine typically starts at puberty but the peak age is considered to be 35 to 45 years. Migraine patients suffer from severe headache along with nausea, vomiting, aura symptoms and photophobia.[4] Pain is the most bothersome and common symptom of migraine. There is much research available for the main causative factor for migraine but still its phenomenon is not fully understood. Previously most commonly used treatments for migraine include triptans, pain killers like NSAIDS, ergot derivatives and antiemetics.[5] Recently it has been proposed that glutamate may also play a role in pathophysiology of pain. That's why glutamate blocking agents like Memantine had been proposed for the management of migraine. Actually memantine neither reduces the levels of glutamate nor decreases its release, rather it reduces the action of glutamate by blocking N-methyl-D-aspartate (NMDA) receptor, so preventing the calcium influx and blocking pathway of pain transmission.[6] Only few studies are available in the literature regarding the role of Memantine for migraine management. Recently published studies have emphasized the role of Memantine for migraine with promising results. Therefore, we planned this study to see the effects of Memantine for migraine management in our population.

Method

This was a prospective observational study conducted at Neurology Department, Services Hospital Lahore over a period of 1 year from Jan. 2019 to December 2019. ,

All the male and female patients, with 18-65 years of age, presenting with migraine were included in the study. The diagnosis of migraine was made according to ICHD-II criteria. Patients already taking memantine or those with other types of headache were excluded from the study. Also pregnant women and migraine patients with any neurological or cardiovascular diseases were excluded. All the included patients were supposed to provide consent for inclusion in the study. All of them were started with memantine as 5mg for 1st week, 10mg for 2nd week, 15mg for 3rd week and 20mg from 4th week. They were maintained at a dose of 20mg till the end of 3 months. All these patients were supposed to maintain a headache diary. They were asked for four questions at the start of the study and at the end of 3 months: 1) Headache frequency per month; 2) Headache severity as per pain rating scale (1-10 as mild to most sever); 3) Level of distress as per distress rating scale (1-10, as mild to most sever distress); and hindrance of activity of daily living as per Migraine Disability Assessment Scale (MIDAS). MIDAS is a self-rated short questionnaire which is used to quantify headache related disability over 3-month period. Also side effects of the Memantine use among study participants were noted. All the data were entered on the proforma. Data were analyzed by descriptive statistics programme of SPSS version 21. Mean and standard deviation (SD) were calculated for qualitative variables while frequency was calculated for quantitative variables. Mean MIDAS score was calculated both before and end of the treatments and student t test was applied for calculating the significance by taking P value as <0.05 significant

Results

A total of 88 patients presenting with headache were evaluated in the OPD. Of all these, 24 were excluded from the study as not fulfilling the inclusion criteria. Treatment was started to 64 patients as per protocol of the study. However 9 patients were lost in the follow up and didn't appear in the OPD. So they were excluded from the study and we were left with 55 patients who completed the study (figure 1). Of these 55 patients, 43 patients (78.2%) were female, while 12 were male (21.8%). The age of the patients ranged from 18 to 63 years. The mean age calculated was 43 ± 11.42 years.

Of all the patients included in the study, 21 patients (38.2%) had migraine with aura, while 34 patients (61.8%) had migraine without aura. The headache frequency of the patients per month significantly reduced after 2 months treatment (figure 2). Also in 76.3% of patients, more than 50% reduction in the frequency of headache was noted after the treatment. The headache severity and level of distress of the patients along the scale before and after the treatments is summarized in figure 3 and 4. The mean MIDAS score before start of the treatment was 81.8±14.76. After 3 months of treatment with Memantine, the MIDAS score found was 15.52±2.84 (P value = <0.05) (Table 1). In our study 21 patients had history of migraine along with aura. After treatment, the aura state was not being experienced by 14 of 21 (66.66%) patients. During whole of the treatment, minimal side effects were encountered by our patients, which included rash, agitation, confusion, dizziness and fatigue. However none of our patients discontinued treatment due to side effects and tolerability of Memantine.

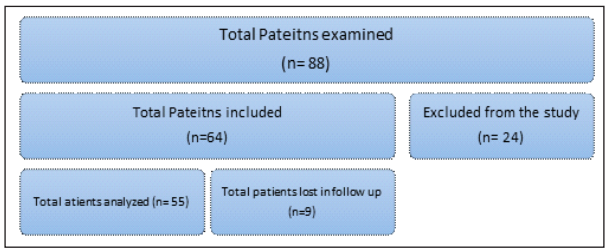

Fig-1: Scheme and protocol of the study.

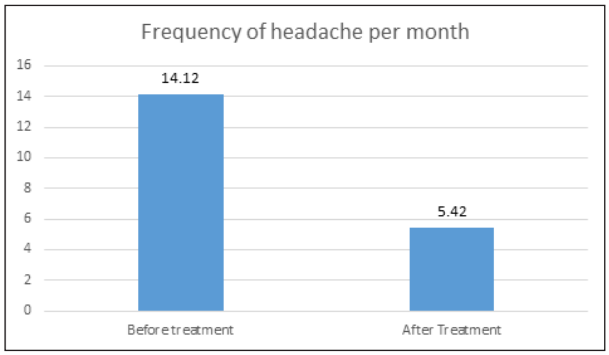

Fig-2: Mean Frequency of headache being experienced by the patients per month.

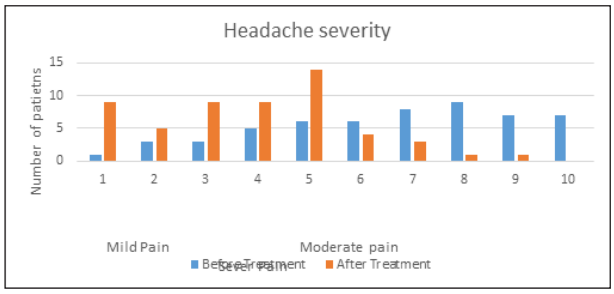

Fig-3: Headache severity according to VAS as experienced by the patients.

Table-1: Means ± SD of MIDAS score of the patients before and after the treatment.

	Before Treatment MIDAS Score (Mean ± SD)	After Treatment MIDAS Score (Mean ± SD)
Q1: On how many days in the last 3 months did you miss work or school because your headaches?	8.945± 3.365	3.436±1.648
Q2: How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches?	26.8±3.73	4.163±2.078
Q3: On how many days in the last 3 months did you not do household work because of your headaches?	11.19±6.543	2.472±1.319
Q4: How many days in the last three months was your productivity in household work reduced by half of more because of your headaches?	214±6.543	4.072±1.766
Q5: On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?	13.2±5.813	1.381±1.327

P Value = <0.005

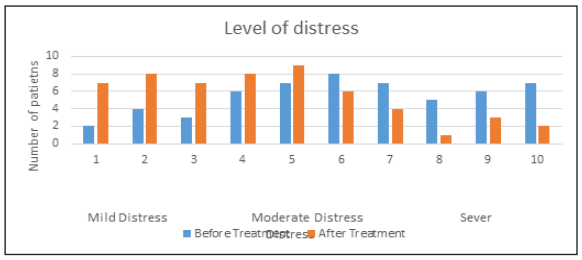

Fig-4: Level of distress as experienced by patients in the study.

Discussion

Memantine has been approved by FDA and is being used for many diseases including headaches, migraine, Alzheimer's disease, alcohol dependence, post-traumatic stress disorder, dementia and obesity.[7-8] Memantine has been proposed for the management of migraine as well as for prevention of migraine. It is because all of these neurologic disorders are thought to be using glutamate for their conduction pathway and Memantine is an NMDA antagonist.[9] During last 5 years, some studies have been conducted on this topic, but still it is a newer drug for neurologists and is not being widely used. Migraine is mainly considered as a disease of females as in our study, 78.2% of patients were females. Similarly Samaan Z et Al conducted a large cohort over 646 patients and they found that there were 82% female patients in the study.[10] In our study, the mean age of the patients was 43 ± 11.424 years. This is also in concordance to the previous large series.[11,12] In our study, patients had high baseline headache frequency which reduced after the memantine therapy. Also in 76.3% of patients, more than 50% reduction in the frequency of headache was noted. Lindelof K et Al. in their placebo-controlled randomized trial found that headache intensity was significantly lower with memantine (3.8) than with placebo (4.1; P = 0.03) on VAS scale.[13] Krusz also reported a 52% and 58% decrease in the frequency of tension-type headache and frequency of migraine respectively from the baseline levels after usage of Memantine.[14] Noruzzadeh R & cooleagues conducted placebo controlled randomized trial on patients with migraine and they found significant decrease in monthly attack frequency in Memantine group than the placebo group. They also found that patients taking memantine had greater reduction in the severity of pain, number of work absence days and disability score than the patients in the placebo group.[15] In our study, memantine was used successfully in all patients with minimal side effects. Jones RW also found in his trial that memantine was well tolerable and fewer side effects were noted. Most commonly noted side effect in that study was dizziness and recurrent headache. Huang L et Al.[16] also found in their systematic review that it was a well tolerated drug in most of the trials with minimal side effects.[17] None of the patient in our study abandoned the protocol because of the side effects. However, Charles A and colleagues mentioned in their study that 6 patients left the treatment because of the side effects which was not the case in our study.[18] As memantine is a relatively newer drug, therefore understanding its pharmacokinetics is important. It has been approved by FDA for usage in USA and is also available in Pakistan. It is usually administered as immediate release formulation and is given twice daily. The maximum recommended dose is 20 mg/day. At the same time, titration of the drug is important.[19] Therefore in our trial, we started the administration of drug as 5 mg, then increasing to 10 mg and 15mg/day. In most of the previous trial same

formulation and dosage has been used as ours.

For analysis of pain score, we used VAS scoring system. It is the most commonly used scale for pain scoring in most of trials. Boonstra AM and colleagues have analyzed VAS and they determined the cut-off level for mild, moderate and sever pain. In their trial, they used 8 different combinations and found that most of the patients labelled VAS ≤3.4 as mild, 3.5-7.4 as moderate and ≥7.5 as severe pain.[20]

Also in our study MIDAS score was calculated for each patient at the start and end of the trial. We found that MIDAS score was significantly low after the treatment of 3 months. Similar findings were noted in another trial which had been conducted in Pakistan. Khalid S et al also found that MIDAS score significantly decreased after 3 months treatment (P= 0.000 (<0.05)).[21]

Our trial had many strengths as it was a prospective trial which has shown evidence based medicine in our own population regarding a newer treatment of migraine. At the same time, it had some limitation. It was not a randomized trial and was conducted at a single center. Therefore we recommend more multi-center randomized trial to unreveal the effects of memantine.

Conclusion

On the basis of this study, we conclude that Memantine is a safe drug and can be used for migraine management. However still further randomized trials with larger sample size are being recommended.

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