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EFFICACY OF MEMANTINE IN TREATING PATIENTS WITH MIGRAINE AND TENSION-TYPE HEADACHE

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ABSTRACT

Objective: To assess the efficacy of Memantine as a preventive and therapeutic intervention for migraine and tension-type headache. **Methods:** This clinical trial was conducted over a period of 3 months. A total of 44 subjects, with diagnosed migraine and/or tension-type headache, presenting to a private neurology clinic in Karachi, Pakistan were selected through purposive sampling technique. Patients were treated with incremental doses of Memantine. Adult patients belonging to both genders were included in the study. Data was analyzed using SPSS version 16.0 and associations were made using Chi square test with p-value of less than 0.05 taken as significant. **Results:** Out of 44 patients, 35 (79.5%) were females and 9 (20.5%) were males which shows a very high occurrence of migraine and tension-type headache in females. Average age was found to be 32.6 ≈ 33 years. Efficacy of the drug was observed to be 81.8% which is significantly high. The baseline MIDAS score when compared with the score at 3-month follow-up by applying Wilcoxon signed rank test showed mean ± S.D (39.52±21.27 vs. 6.72±6.41) where p=0.000 (<0.05) which shows a highly significant result. All 44 patients were known cases of migraine while 25% (11) of them also suffered from tension-type headache. Patients were treated with incremental doses of Memantine and were observed for the efficacy of the drug. Patients maintained their diaries of intensity of pain, distressing influence of the pain and how it hindered their daily routine. Results showed that intensity of pain decreased significantly by the end of the 3rd month of treatment and majority of the patients felt less distressed on their final follow-up visit. By the end of the 3rd month, the level of hindrance in the daily routines of the patients caused by the headache also fell significantly. **Conclusion:** Memantine has significant beneficial effects in reducing intensity of pain and disability in patients with migraine and tension type headache.

Keywords: Memantine, Migraine, Tension-type headache, Efficacy, Headache.

BACKGROUND

Memantine, an N-methyl D-aspartate (NMDA) receptor antagonist, works through its intrinsic blockade of afferent signals of pain transmission, known as the glutamate system, which plays a major role in pathophysiology of tension-type headache (TTH) and migraine [(1)]. Memantine works as an uncompetitive, voltage-dependent, low affinity, open channel antagonist. By binding to the NMDA receptor with a higher affinity than Mg2+ ions, Memantine inhibits the prolonged influx of Ca2+ ions, which forms the basis of neuronal excitotoxicity. Most importantly, its dissociation rate is relatively faster which allows it not to accumulate substantially in the synaptic channels, hence, it does not interfere with the normal synaptic transmission [(2,3,4,5)]. Therefore, it can be used as an effective modality in prophylaxis and treatment for chronic pain disorders including tension-type headache and migraine. During the recent decade, Memantine has evolved as a revolutionary drug in the treatment of chronic pain states. Its efficacy as a neuroprotective drug has been demonstrated through various researches [(1,6,7)]. Glutamate and other excitatory neurotransmitters have been highlighted to be involved in transmission of signals to spinal cord or brainstem in chronic pain states. Similarly, these neurotransmitters are thought to be involved in potentiation and augmentation of the pain transmission cascade in chronic headache conditions [(1)]. Memantine has also shown potential in addressing the issues of complex regional pain syndrome and phantom limb pain, which suggests that its effectiveness in relieving pain depends on the kind of pain under consideration [(8)]. Cognitive problems have often been reported by patients with chronic pain disorders. Memantine, being a glutamate receptor antagonist, has the capacity to tackle both of these problems [(9)]. Furthermore, in several clinical trials, Memantine has shown very low incidents of adverse effects [(10,11)]. Studies have proven that Memantine has

its excellent effects on D2 receptors as well, preventing its sensitization during a manic attack, hence it can be used as drug of choice for bipolar disorder [12]. Recent works are being done to evaluate its effectiveness in neurocognitive disorders such as Alzheimer's disease [10,11,13]. The aforementioned wide variety of uses of Memantine in the field of medicine has greatly increased the interest of researchers in this revolutionary drug. To the best of our knowledge, no study has been conducted in our population about the use of NMDA antagonists that could be of major interest in regards to the pathophysiology and future treatment of Migraine, TTH and other chronic pain disorders.

OPERATIONAL DEFINITIONS

MIGRAINE: A primary headache disorder that is benign and recurrent, often life-long, and characterized by attacks. Attacks include features such as Headaches, most often described as pulsating, throbbing, unilateral and aggravated by minor movement and routine physical activity; typically lasting hours to 2-3 days Nausea, photophobia and phonophobia Attack frequency ranges from once a week to once a year [14]

TENSION-TYPE HEADACHE: A primary headache disorder characterized by tight, band-like headaches that occur bilaterally. These headaches may be related to stress or associated with musculoskeletal problems in the neck. They may last a few hours or persist for several days with or without fluctuations.

Variable	Frequency (%)	Mean ± S.D	Range(Min/max)
Gender Male Female	9 (20.5%) 35 (79.5%)		
Age		32.6±10.32	18/65
Efficacy of Memantine	36 (81.8%)		
Diagnosis Migraine Migraine + TTH Migraine changing to seizures Others	20 (45.45%) 11 (25%) 3 (6.81%) 10 (22.7%)		
MIDAS Variables Missed work or school (no. of days)		6.81±7.15	0/30
Productivity at work/school reduced by half (no. of days)		6.88±5.52	0/20
Could not perform household chores (no. of days)		9.97±6.36	0/33
Productivity reduced by half in household work (no. of days)		10.52±6.06	3/32
Missed leisure activities		5.86±4.84	0/20
Average headache days		14.39±6.41	1/32

TABLE 1: Baseline characteristics

MATERIALS AND METHODS

A total of 44 subjects, with diagnosed migraine and/or tension-type headache, presenting to Neuro Clinic and Care, a private neurology clinic in Karachi, Pakistan were selected through purposive sampling technique. Data was collected over a period of three months between January 2015 and March 2015.

INCLUSION CRITERIA INCLUDED: Males and females aged between 18 and 65 years Diagnosis of Migraine using International Headache Society Criteria for Diagnosis of Migraine[15] Diagnosis of TTH using International Headache Society Criteria for Diagnosis of TTH[15] Signature of Informed Consent Form. In case of females of childbearing age, commitment not to become pregnant during the entire duration of the study.

EXCLUSION CRITERIA INCLUDED : Patients below the age of 18 and above the age of 65. Patients undergoing drug treatment for migraine or TTH. Patients already receiving treatment will stop treatment and a washout period of one week will be performed. During the washout period the patient may take, if necessary, analgesics such as Tramadol or Acetaminophen. Patients currently taking Memantine or having taken Memantine during the 2 months prior to recruitment. Another Axis I psychiatric disorder using Structured Clinical Interview for DSM-IVAxis I Disorders (SCID-I) that may interfere with adherence to the study protocol (e.g. alcohol and/or substance abuse/dependence, schizophrenia, chronic delirium, acute depression etc.) Pregnancy or breast-feeding. Hypersensitivity to the active ingredient, Memantine. Medical conditions that require special precautions when administering Memantine according to the summary of product characteristics: a) epilepsy b) circumstances that may cause high urine pH owing to Proteus urinary tract infection or renal tubular acidosis c) recent myocardial infarction, d) congestive heart disease and e) uncontrolled arterial hypertension. Clinically significant and active evidence of liver or kidney disease, hematological, respiratory, endocrine or cardiovascular disorders. Use of prescription drugs that may cause drug interactions with Memantine: NMDAR antagonists (amantadine, ketamine, dextromethorphan), L-Dopa, dopamine agonists and cholinergic agonists. Use of non-permitted concomitant medication during the week prior to the recruitment or where the patient is expected to require treatment with such drugs: antidepressants (duloxetine, venlafaxine, mirtazapine, bupropion, SSRI, etc), analgesics (pregabalin, gabapentin, opiates, etc).

Each patient diagnosed to have migraine and/or TTH coming to the outpatient department was explained about the purpose of the study including the risks and benefits of participation in the study. After obtaining signed consent, intervention was started. Patients received 20 mg of Memantine (2 tablets of 10 mg

each).

The dose of 20 mg was reached following this schema:
1st week: 5 mg daily
2nd week: 10 mg daily
3rd week: 15 mg daily

From the 4th week up to the 12th week: 20 mg daily Patients kept headache diaries for migraine and TTH, as well as pain scores. Patients were followed up initially at 1st week, 2nd week, then every month for a total of three months. On each follow-up visit, pain rating scale and MIDAS questionnaire was filled and patients were observed for the efficacy of the drug.

Variable	At baseline	At 3 month follow-up
	Frequency (%)	
How intense is your pain now?		
No pain	0	1 (2.3)
Mild	0	15 (34.1)
Moderate	4 (9.1)	19 (43.2)
Severe	15(34.1)	8 (18.2)
Extreme	25(56.8)	1 (2.3)
How intense was your pain on average last week?		
No pain	0	1 (2.3)
Mild	0	11 (25)
Moderate	13 (29.5)	18 (40.9)
Severe	15 (34.1)	13 (29.5)
Extreme	16 (36.4)	1 (2.3)
How distressing is your pain now?		
No distress	0	3 (6.8)
Mild	2 (4.5)	14
Moderate	(31.8)	
Severe	6 (13.6)	20
Extreme	(45.5)	
	25 (56.8)	6 (13.6)
	11 (25)	1 (2.3)
How distressing was your pain on the average last week?	0	2 (4.5)
No distress	3 (6.8)	16 (36.4)
Mild	7 (15.9)	18 (40.9)
Moderate	25 (56.8)	7 (15.9)
Severe	9 (20.5)	1 (2.3)
Extreme		
How much does your pain interfere with your normal activities?	0	2 (4.5)
No interference	1 (2.3)	22 (50)
Mild	12 (27.3)	14
Moderate	(31.8)	
Severe	26 (59.1)	5 (11.4)
Extreme	5 (11.4)	1 (2.3)

Variables	Mean±S.D	p-value
Baseline score vs. follow-up at 3 months	39.52±21.27 vs. 6.72±6.41	0.000

TABLE 2: Intensity of pain, frequency of distress and interference at baseline and at 3 months follow-up

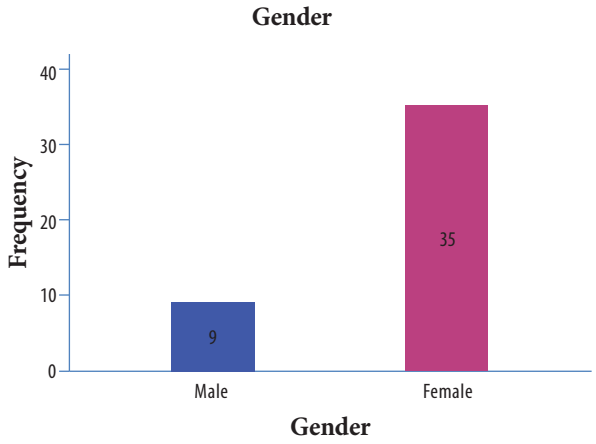
OUTCOME MEASURES

Improvement in clinical variables. Intensity of pain. It will be evaluated using Pain Rating Scale. It is a horizontal line, 10 cm in length, anchored by word descriptors at each end (no pain and extreme pain). Level of distress caused by the pain. It will be evaluated with Pain Rating Scale. It is a horizontal line, 10 cm in length, anchored by word descriptors at each end (no distress and extreme distress). Interference of pain with normal daily activities. It will be evaluated with Pain Rating Scale. It is a horizontal line, 10 cm in length, anchored by word descriptors at each end (no interference and extreme interference). Disability caused by the pain. It will be evaluated with the Migraine Disability Assessment Test (MIDAS). MIDAS is a 5-item questionnaire to measure the health status and level of disability caused by the pain in patients with headache disorders.

INTERPRETATION: 0-5 – MIDAS Grade I (Little or no disability) 6-10 – MIDAS Grade II (Mild disability) 11-20 – MIDAS Grade III (Moderate disability) ≥ 21 – MIDAS Grade IV (Severe disability).

SPSS version 16.0 was used for statistical analysis. Separate frequencies and percentages were calculated for categorical variables. Association was assessed through Chi square test and p-value ≤ 0.05 was taken as significant.

FIGURE 1: GENDER DISTRIBUTION AMONG SUBJECTS



RESULTS

Out of 44 patients, 35 (79.5%) were females and 9 (20.5%) were males which shows a very high occurrence of migraine and tension-type headache in females (Figure 1). The mean age of the subjects was found to be 32.6 ≈ 33 years. Our subjects were classified according to the type and nature of chronic headache. Comprising of migraine alone, migraine along with tension-type headache, migraine changing to seizures and others, in coherence with other studies.16 All 44 patients were known cases of migraine while 25% [11] of them also suffered from tension-type headache as shown in Table 1. An initial daily dose of 5 mg of Memantine was started for 1 week with weekly dose increase of 5 mg up to a maximum dose of 20 mg per day, as tolerated. Patients were asked to maintain a headache diary of intensity of pain, distressing influence of the pain and how it hindered their daily routine in order to keep an account of

effectiveness of the drug in every individual. On each follow-up visit, pain rating scale and MIDAS questionnaire was filled and patients were observed for the efficacy of the drug. Efficacy of the drug was found to be 81.8% which is significantly high. The baseline MIDAS score when compared with score at 3-month follow-up by applying Wilcoxon signed rank test showed mean ± S.D (39.52±21.27 vs. 6.72±6.41) where p=0.000 (<0.05) which shows a highly significant result as shown in Figure 2. Results in Table 2 show that intensity of pain decreased significantly by the end of the 3rd month of treatment, with only 2.3% of the patients complaining of extreme pain at the final follow-up at 3 months while 56.8% of the patients complained of extreme pain at the initial visit. Majority of the patients felt less distressed on their final follow-up visit at 3 months. 6.8% of the patients had no distress or discomfort at the final follow-up. By the end of the 3rd month, the level of hindrance caused by the headache in the daily routines of the patients also fell significantly, with only 2.3% of the patients complaining of extreme interference of pain with normal daily activities at the 3-month follow-up.

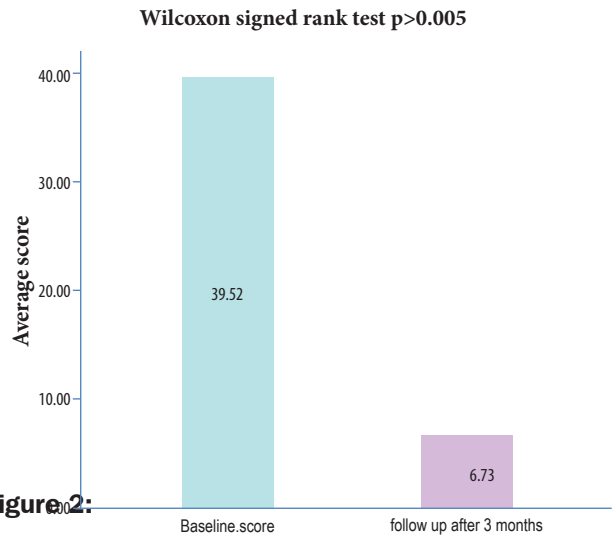


Figure 2:

DISCUSSION

This study sought to explain the efficacy of Memantine in the treatment of migraine and tension-type headache. A number of studies have elucidated that Memantine, a low-affinity antagonist to NMDA glutamate receptors that are thought to be intrinsic to pain transmission, is effective in the treatment and prophylaxis of migraine and tension-type headache.[1,6,9,16] Memantine works by blocking NMDA glutamate receptors that are excitatory amino acids and play an intrinsic role in pain transmission, long-term potentiation and central sensitization. Therefore, blockade of NMDA receptors helps in reducing the central barrage of afferent signals that may be involved in the maintenance of chronic headache states. As in other similar researches [1], the participants in our study mainly comprised of females (79.5% vs 20.5%), proving a worldwide female dominance in incidence of migraine and tension-type headache. The ages of our patients ranged from 16 to 65 years. It is reasonable to expect migraine symptoms to improve as patients get older, however, many people continue to have migraine attacks in older age and considerable number of people with migraine in later life exist in many populations worldwide. According to The Migraine Trust, "many migraine sufferers contacting The Migraine Trust have said that they expected their migraines to get better as they got older. Unfortunately this is not the case for everyone. There are many people with migraine in their 60s, 70s, and 80s.[17] Dr. Vincent Martin, professor of medicine and co-director of the Headache and Facial Pain Program at the University of Cincinnati says headaches increase by 50 to 60 percent in women with migraine during perimenopausal and menopausal time periods.[18] Biqal and Rapoprt, in their study on Memantine in the preventive treatment of refractory migraine, reported a decrease in headache frequency from 21.8 days at baseline to 16.1 days at 3 months (p <0.01) as well as a significant reduction in mean disability scores at the final follow-up at three months which correlates with the results of our study[9]. In our study, the baseline disability score when compared with the score at 3-month follow-up by applying Wilcoxon signed rank test showed mean ± S.D (39.52±21.27 vs. 6.72±6.41) where p=0.000 (<0.005) which shows a highly significant result. Similarly, a randomized, double-blind, placebo-controlled, cross-over trial demonstrated a significant reduction in intensity of headache on a 0-10 verbal rating scale[16]. In our study, the intensity of headache decreased considerably by the end of three months with only 2.3% of the patients complaining of extreme pain at the final follow-up visit at 3 months compared to 56.8% of the patients complaining of extreme pain at the initial visit. Furthermore, at the final follow-up visit, 2.3% of the patients were entirely relieved of the pain. In his preliminary open-label study conducted on 30 patients with chronic refractory headache disorders, Krusz reported a 58% and 52% decrease from the baseline in the frequency of migraine and tension-type headache respectively at the end of one month, which gives a similar proportion as in our study [1]. As per patients self-reporting in their headache diary, the interference of headache with routine work markedly reduced in

frequency from 59% to 40% ($p<0.005$). When patients reported at 3 months follow-up, there was a significant reduction in frequency of occurrence of symptoms, statistically proven as 39.52±21.27 vs. 6.72±6.41 (baseline vs. follow-up). According to a meta-analysis, Memantine may be a reasonable option for the prevention of primary headache disorders as it lowered the frequency and intensity of migraine headaches and demonstrated only few adverse effects, which is in correlation with our study [19]. For Memantine to be utilized as an abortive treatment, more evidence in the form of randomized, double-blinded, placebo-controlled clinical trials comparing Memantine with a standard abortive treatment will be needed. In our study, none of the patients developed significant adverse effects to warrant exclusion from the study. Efficacy of the drug, in our study, was observed to be 81.8% at the end of three months but more Phase 2 and 3 clinical trials are needed before the definitive duration of treatment can be established.

CONCLUSION

Memantine is an effective drug for the prophylactic treatment of migraine and tension-type headache in terms of reducing intensity of pain and improving the quality of life. A randomized, placebo-controlled, double-blind clinical trial is needed to confirm our observations.

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Author's contribution:

Sameen Khalid: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Bashir Soomro: Study concept and design, protocol writing, data analysis, manuscript writing, manuscript review

Samreen Mahmood: Data collection, data analysis, manuscript writing, manuscript review

Aamer Abbass: Data analysis, manuscript writing, manuscript review