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IMPACT OF MEMANTINE ON QUALITY OF LIFE IN MIGRAINE PATIENTS: A DOUBLE BLIND PLACEBO CONTROLLED CLINICAL TRIAL.

Neurology

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ABSTRACT

Background and objective: Migraine is a primary headache disorder that puts a huge burden on patients normal functioning and productivity because of its abundant prevalence and young age of onset. Hence any drug study on migraine should necessarily evaluate the drug's efficacy in improving patients Quality Of Life (QOL) apart from reducing migraine frequency. We previously reported that memantine 10 mg per day produced a statistically significant reduction in mean monthly migraine headache days. To define yet more clearly the utility of memantine in the treatment of migraine, we evaluated secondary endpoints namely QOL from the trial.

Methods: It was a randomized, placebo controlled double blind study including adult patients with 3-12 migraine headaches for last six months. Patients received memantine(10mg/day, once a day) or placebo for the period of 24 weeks after a wash out period. Along with Migraine frequency per month, the 50% responder rate, rescue medication use and adverse events, mean MIDAS(Migraine Disability Assessment) score was recorded every 4 weeks.

Results: The mean MIDAS score for memantine receiving patients was; at baseline; 12.00 (±1.04) vs. at week 24; 3.64 (±0.42) and placebo receiving patients was at baseline; 12.55 (±0.89) vs. week 24; 7.76 (±0.66). The MIDAS score by week 24 was significantly less (p=0.0001) in patients receiving memantine than that of placebo receiving patients

Conclusions: In addition to significantly reducing mean monthly migraine headache days, treatment of migraine with memantine was indeed effective with regard to clinically relevant Quality of life measures.

KEYWORDS

Migraine, Memantine, Quality of Life, MIDAS

INTRODUCTION

Migraine is a disabling, common primary headache disorder that has a significant impact on daily activities. To understand its impact, data about prevalence and age of onset will provide a clear picture. Lifetime prevalence of migraine is as high as 14%, with a male to female ratio that varies for adults from 1:2 to 1:3[1]. Current prevalence of migraine was estimated at 10%[2]. The most common age of onset of migraine is in the second and third decades of life. Because of young age of onset and significant prevalence, it exerts a huge burden on patients normal functioning and productivity[3]. According to WHO, it is 19th amongst the diseases causing disability[4].The total direct and indirect costs associated with migraine is nearly equal to the cost associated with all cerebrovascular disease[5,6].

In the revised International Classification of Headache Disorders (ICHD-3), migraine diagnostic criteria includes unilateral location, pulsating quality, moderate or severe intensity, nausea and/or photophobia with phonophobia and aggravation by or causing avoidance of, routine physical activity[7]. Hence unlike Tension type headache where patient can do routine physical activity, migraine patients cannot do their physical activities thereby affecting their quality of life.

Hence any migraine treatments main focus should not only be to reduce migraine monthly days but also to improve patient's quality of life. Specifically Migraine related disability assessment is essential to provide a rational basis for treatment. MIDAS (Migraine Disability Assessment Questionnaire) is a validated headache specific tool to assess migraine related disability[8,9].

We recently published the results of a randomized, double blind, placebo-controlled study which demonstrated that treatment of migraine with memantine 10 mg per day resulted in statistically significant reductions in mean monthly migraine headache days and the drug was found to be safe and generally well-tolerated[10]. We present herein results for quality of life from the study. The main aim of this article is to assess the efficacy of memantine in reducing the headache related disability.

METHODS

This was a randomized, double blind, parallel interventional study. It was conducted at the Headache Clinic, Department of Neurology in a tertiary care hospital in Tamilnadu. The study was conducted over a six month period. Sixty patients with migraine as assessed by International Headache Society (IHS) criteria, for at least 6 months before screening were recruited for the study. Patients with 3-12 migraine (not more than 15 headache days) were included. Patients having headache not related to migraine (episodic tension or sinus headaches) were excluded. If headache didn't respond to more than 2 migraine preventive medications, they were excluded. Pregnant/breast feeding women, patients with Medication overuse headache, severe medical illness, renal insufficiency, hepatic problems, and hypersensitivity were also excluded. Study was approved by the Institutional Ethics Committeeand conducted according to ICH good clinical practice guidelines and the principles of the Declaration of Helsinki. The trial was registered prospectively in ICMR'S clinical trials registry of India (CTRI/2013/11/004172) before the recruitment of the patients. Along with Migraine frequency per month, the 50% responder rate, rescue medication use and adverse events, MIDAS Score was recorded every 4 weeks. Further full details of the clinical study design, methodology, and subject eligibility criteria previously have been published[10].

RESULTS

We utilized Migraine Disability Assessment Scale (MIDAS) to evaluate effect of memantine on disability and quality of life due to migraine headache (**table 1 and figure 1**). By week 12 of the treatment, the mean MIDAS score in memantine receiving patients was significantly less than that of placebo receiving patients. This trend continued till the end of the treatment by week 24. The mean MIDAS score for memantine receiving patients was; at baseline; 12.00 (±1.04) vs. at week 24; 3.64 (±0.42) and placebo receiving patients was at baseline; 12.55 (±0.89) vs. week 24; 7.76 (±0.66). The MIDAS score by week 24 was significantly less (p=0.0001) in patients receiving memantine than that of placebo receiving patients. Hence, Memantine significantly improved MIDAS score and quality of life in patients with migraine headache.

Table 1 Effect of memantine on MIDAS score (mean±SEM)

Duration of treatment	Memantine	Placebo	T-value	P-value
Base line	12.00 (±1.04)	12.55 (±0.89)	-0.405	0.687
12 weeks	7.18 (±0.67)	9.38 (±0.64)	-2.368	0.021
24 weeks	3.64 (±0.42)	7.76 (±0.66)	-5.267	0.0001

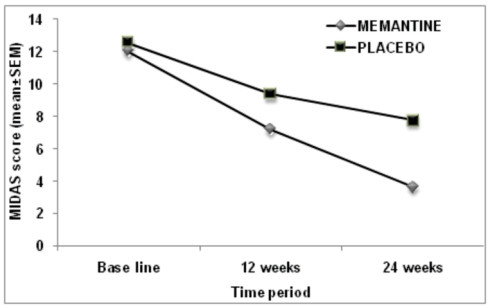

Figure 1 Effect of memantine on MIDAS score

DISCUSSION

A Principal determinant of efficacy of any migraine preventive treatment is how much that drug reduces migraine frequency. This is exemplified by the International Headache Society's guidelines which recommend using reduction of migraine attacks over a 28-day period as a primary efficacy measure in clinical trials of preventive migraine treatment[11].Previously published results from our study showed that treatment with memantine significantly reduced migraine monthly days[10]. But in clinical practice, an equally important determinant of a drug's efficacy is its ability to reduce disability and to restore function[12]. Hence any drug study on migraine should necessarily evaluate the drug's efficacy in improving patients QOL. The current report included analyses of specific migraine related QOL measures such as MIDAS Score. Here we are presenting the results of memantine in improving the quality of life.

Migraine patients not only have decreased productivity at work but also miss family and social activities. They also have apprehension about having next attack[13]. WHO in 2004 placed migraine at 19th among diseases causing disability[14]. They also equated a day of worst migraine to the disability associated with a day of quadriplegia or psychosis[15].Since Migraine is three times more commoner in females and usually is at its worst in between 35 to 45 years[16], it is a big burden for them as they have not only to care for their families but also to make their carriers in these productive years of their life[17].

The prevalence of migraine varies from 5 % in Africa to 15% in Europe[2]. In USA, functional impairment occurs in 91% of migraine patients[18]. Indian studies in migraine are less with one study in Karnataka putting migraine prevalence at 23%[19]. Furthermore there is a lack of data from India on the impact of migraine on health-related quality of life (HRQoL).In a study by Sharma et al, HRQoL is significantly reduced in Indian migraine patients compared to healthy controls[20]. Hence assessing the impact of migraine and its treatment on patients QOL might help as a guide to healthcare policy making.

Various questionnaires have been developed to assess quality of life in migraine patients such as migraine-specific quality of life questionnaire (MSQ) that evaluates quality of life in migraine patients[21,22], migraine severity (MIGSEV) scale that accesses severity of pain in different attacks[23], headache impact test (HIT-6) that measures impact of headache during one month[24], and migraine disability assessment scale (MIDAS) that measures disability related to migraine in a three-month period[25].The migraine disability assessment (MIDAS) questionnaire has been developed by Lipton et al[25]. The MIDAS questionnaire, is the most frequently used disability instrument in migraine research and clinical practice[25,8,9]. There is extensive evidence for reliability and validity of the MIDAS[8,9]. It is a self-administered questionnaire consisting of five items that assess days of missed activity or substantially reduced activity due to headache in three domains—schoolwork/paid employment, household work or chores, and non work (family, social and leisure) activities. Because each day of headache could result in lost time in each of the three domains, the maximum MIDAS score per day is 3 and the maximum score over 3 months is 270.

In our study, mean MIDAS score decreased by week 12 of the treatment and this trend continued till the end of the treatment by week 24. The mean MIDAS score in memantine receiving patients was significantly less than that of placebo receiving patients.

A few clinical studies evaluated efficacy of memantine for migraine patients. In Charles[26] retrospective study, MIDAS was not used. To assess the QOL they only assessed the patient responses to the analogue scale of "How you felt and how well you functioned overall while taking memantine as compared with before you took it." In Bigal[27] et al study, mean MIDAS scores were significantly reduced at 3 months, compared with baseline (36.6 vs 54.9, $P < .01$). In Davood Kashipazha[28] et al study, at the end of 3 months the MIDAS score in the memantine group decreased to 17.59 ± 5.52 from 40.04 ± 13.66 and in the placebo group decreased to 24.63 ± 14.77 from 39.37 ± 15.35, which was significantly lower in the memantine group. ($p = 0.024$).

Since number of studies assessing the effect of memantine on QOL is less, we also compared with studies of other antimigraine drugs on QOL. A randomized, double blind, placebo controlled study of Topiramate for the prevention of headache in chronic migraine reported that there is a reduction in MIDAS score from the baseline score of 67 to 41 in the treated group while for placebo similar scores increased from 61 to 41[29]. Another multi-centre trial by Silberstein et.al., showed that the mean MIDAS score reduced from 64.4 (46.6) to 31.4 (53.8) in the test group while in placebo group mean MIDAS score reduced from 62.2(43.4) to 21.0 (52.2), indicating that the Topiramate treated group showed a greater improvement[30]. So in conclusion, our study also showed results comparable to previous studies though our baseline MIDAS score was less.

The limitation of our study is taking MIDAS Score only as the sole criterion for assessing QOL. Another limitation is size and duration of the study. A large and long-term study with multiple QOL questionnaires is advocated to further validating the efficacy of memantine in improving QOL in migraine patients.

In summary, this study confirms that memantine not only decreases migraine frequency but also improves their Quality of life. Probable explanation for the improvement of Quality of life could be attributed to the general reduction in the frequency and severity of headaches due to Memantine treatment.

CONCLUSION

Evaluation of the additional therapeutic effects of preventive migraine management to include improvements in patients' Quality of life is an increasingly important component of efficacy and may broaden the scope of management strategies that decrease the overall burden of the migraine. The results of this study expand the usage of Memantine as a preventive treatment in migraine patients.

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