Original Article

Memantine Ameliorates Migraine Headache

Sundar Shanmugam, Kranthi Karunaikadal[1], Sathyanarayanan Varadarajan[2], Muthuraj Krishnan[3]

Departments of Neurology and [1]Pharmacology, Sri Ramachandra Medical College, Departments of [2]Pharmacology and [3]Neurology, SRM Medical College, Chennai, Tamil Nadu, India

Abstract

Background and Objective: A significant number of migraine patients do not find effective and safe treatment to reduce the frequency and severity of their migraine attacks. Hence, a need for newer therapeutic agent exists. In this study, we examined the efficacy and safety of memantine for the treatment of migraine. **Materials and Methods:** It was a randomized, placebo-controlled, double-blind study including adult patients with 3–12 migraine headache for the last 6 months conducted in India. Patients received memantine (10 mg/day, once a day) or placebo for the period of 24 weeks after a washout period. Migraine frequency per month, the 50% responder rate, rescue medication use, and adverse events were recorded every 4 weeks. **Results:** Among 81 patients screened, 60 were enrolled for the study. Thirty patients received memantine and other 30 received placebo. Data were analyzed for 28 patients in memantine group and 29 patients in placebo group. At the baseline, all the parameters were similar in both groups. By 24 weeks, migraine frequency/4 weeks was memantine group versus placebo; 2.57 (±0.38) versus 5.07 (±0.69), $P = 0.003$ and rescue medication use was 0.75 (±0.23) versus 3.72 (±0.63) $P = 0.0001$. The 50% responder rate was 85.7% versus 51.7% ($P = 0.005$). Only a few mild adverse events were recorded in both the groups. No severe adverse events and death were recorded during the study. **Conclusion:** Memantine (10 mg oral, once daily) is effective, well tolerated, and safe for patients with migraine.

Keywords: Antiglutamate drugs, International Headache Society criteria for migraine, memantine, migraine

Introduction

Among the various causes of headache, migraine is one of the most common. Overall, migraine has a variable prevalence worldwide. In Europe and USA, 1-year period prevalence of migraine in adults is estimated at 10%–15%.[1] A migraine attack is a throbbing or pulsating headache which is unilateral and may involve nausea, vomiting, and sensitivity to light or sound.[2] Migraine headache leads to significant disability. It adversely affects the daily activities and work-related productivity for the patients.[3] Majority of the migraine patients in India do not consult a physician. Moreover, among patients who are treated for migraine, less than one-third report consistently effective results with their current treatment which include over-the-counter analgesics.[4] Despite recent developments in the understanding of pathophysiology, epidemiology, and genetics of migraine, many patients with migraine are not diagnosed correctly and many of them are treated suboptimally. Although multiple preventive medications for migraine are available, a significant number of patients are unable to find effective regimen to reduce the frequency and severity of their migraine attacks. Migraine remains one of the most underrecognized, underdiagnosed, and undertreated conditions.

Growing number of researchers consider migraine as an episodic disorder of brain excitability. N-methyl-d-aspartate (NMDA) receptor antagonists inhibit the cortical spreading depression (CSD), which is considered as an underlying mechanism of migraine. The precise mechanistic links between CSD and migraine require in-depth investigation. However, recent evidence suggest that CSD can also initiate migraine headache.[5] CSD, equivalent to the aura phase of migraine, activates the trigeminal nociceptive pathway in the brainstem and may precipitate the headache phase.[6,7] In patients with headache induced by glyceryl trinitrate, the brain stem region is activated. However, it is not activated in normal people, suggesting a migraine-related sensitivity.[8] This sensitivity could make migraine patients more susceptible to the effects of CSD.

The cellular mechanisms underlying the initiation and propagation of CSD remain enigmatic.[9] Two hypotheses to describe CSD propagation have been proposed. The first is Grafstein's potassium hypothesis which suggests that K+ ions are released during neuronal depolarization and accumulate in the interstitial spaces. Excessive K+ ions further depolarize the surrounding cells, leading to another wave of CSD.[10] The second hypothesis, proposed by van Harreveld suggests that glutamate induces CSD when applied to the cortex. However, both the mechanisms may contribute in CSD prorogation. Hence, glutamate, the primary excitatory neurotransmitter in the central nervous system presents an appealing target for therapeutic strategies to treat migraine.

Address for correspondence: Dr. Sundar Shanmugam, Department of Neurology, Sri Ramachandra Medical College Hospital, Porur, Chennai - 600 116, Tamil Nadu, India.
E-mail: drradnus@gmail.com

DOI: 10.4103/aian.AIAN_294_18

Thus, we hypothesized that antiglutamate drugs might reduce migraine effectively. Memantine is a noncompetitive antagonist of the NMDA-type glutamate receptor. It interacts with the Mg^{2+} binding site of the channel to prevent excessive activation while sparing normal function.[11] Memantine was approved by the US Food and Drug Administration in 2004, for the treatment of cognitive impairment in Alzheimer's dementia. Numerous clinical studies have shown that memantine is well tolerated and safe with a few side effects of headache or dizziness which are usually mild and reversible.[12] A few small clinical studies showed a moderate clinical response to memantine in migraine patients. Hence, it is warranted to conduct a large randomized, controlled clinical study to evaluate efficacy and safety of memantine evaluating multiple aspects of migraine. In this randomized, placebo-controlled study, we evaluated efficacy and safety of memantine as a preventive medication for migraine. The primary objective of this study was to evaluate the efficacy of memantine to reduce the migraine frequency. In addition, we analyzed the effect of memantine on rescue medication use and 50% responder rate. The secondary objective of the study to evaluate the safety of memantine.

Materials and Methods

Patient population

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 Tamil Nadu. The study was conducted over a 6-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 did not respond to more than two migraine preventive medications, they were excluded. Pregnant/breastfeeding women, patients with medication overuse headache, severe medical illness, renal insufficiency, hepatic problems, and hypersensitivity were also excluded. The study was approved by the Institutional Ethics Committee and 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.

Intervention and treatment

Eligible patients after conforming to inclusion and exclusion criteria entered a washout period of 28 days. During the washout period preventive migraine medications were reduced and stopped. Following this period, a baseline phase of 3 months was established during which patients were allowed to take only rescue medications. Data regarding 4-week frequency (monthly) and number of days of rescue medication were collected during baseline period. After completion of baseline period, patients were randomized to one of the two groups: intervention and placebo groups.

- Group 1 – Intervention: Memantine hydrochloride tablet (Admenta, SUN Pharma, India) 10 mg was given orally once daily for 24 weeks
- Group 2 – Placebo: A look-alike sugar pill was given orally once daily for 24 weeks.

Figure 1 shows a flow diagram of the study.

Data collection

The 28 days (monthly) migraine frequency, number of days of rescue medications intake, and adverse effects were all recorded by each patient in a diary, which was then transcribed into patients case record form at each clinical visit. The transcription was performed on the 29th day. Blood investigations and physical examination were performed at the first and last visit. Liver function test was performed on first, third, and last visit.

Statistical analysis

Descriptive data were analyzed and presented as frequency, percentages, mean and standard deviation, and standard error. Inferential statistics including Chi-square test and unpaired *t*-test were used for analysis. The analysis was performed using statistical software package IBM SPSS Statistics 21.0

Results

Patient's demographics

Eighty-one patients were assessed for eligibility; 21 patients were excluded as 14 patients did not meet inclusion criteria and 7 patients declined to participate. A total of 60 patients (3–12 migraine days/month) met the inclusion criteria and were enrolled for the study. They were randomly divided into two groups. In Group 1, 30 patients received memantine and in Group 2, 30 patients received placebo. Two patients of memantine group and 1 patient of placebo group was lost to follow-up.

Fifty-seven patients were included in follow-up analysis. Among 28 patients of memantine group, 10 were male and 18 were female. In placebo group, 9 were male and 20 were female. Among all patients, 35 patients were in the age group of 18–30 years, 18 patients were in the age group of 31–40 years and 4 patients were in the age group of 41–55 years among all patients, 29 were unemployed and 28 patients were employed. Among 28 patients in memantine group, only two patients had migraine with aura. In placebo group, only one patient had migraine with aura. Among all patients, 12 patients had migraine for <1 year, 34 patients for 1–5 years, 9 patients for 6–10 years, and 2 patients had migraine for more than 10 years.

Effect of memantine on migraine frequency

We evaluated the efficacy of memantine for reducing migraine headache episodes and analyzed mean number of days with migraine episode every 4 weeks till 24 weeks after the initiation of treatment [Table 1 and Figure 2]. We observed a decline in the mean number of migraine days till the 12th weeks after the commencement of treatment in both the groups (memantine:

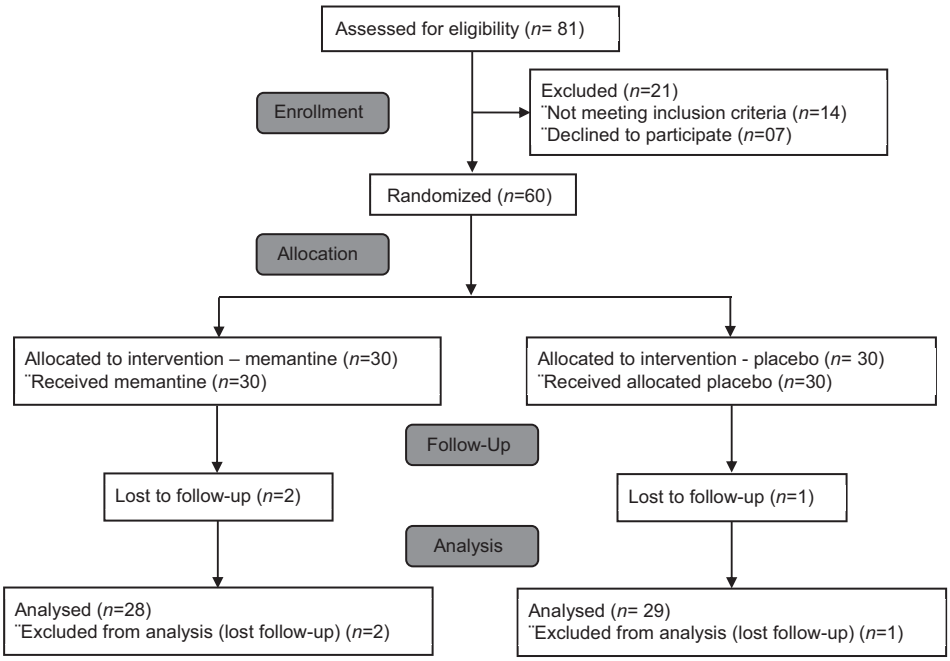

Figure 1: Consort flow diagram

10.79 days to 5.18 days and placebo: 10.14 days to 6.03 days). This trend was continued in memantine group till the end of the study by 24th week and the frequency of migraine days was reduced up to 4 times by week 24 after the treatment with memantine (10.79 days at baseline vs. 2.57 days at week 24). On the contrary, in placebo group, no decline in migraine days was observed from 12- to 24-week period posttreatment (6.03 days at week 12 vs. 5.07 days at week 24). Moreover, migraine frequency was significantly less ($P = 0.003$) in memantine-receiving patients 2.57 (±0.38) at week 24 as compared to placebo-receiving patients 5.07 (±0.69).

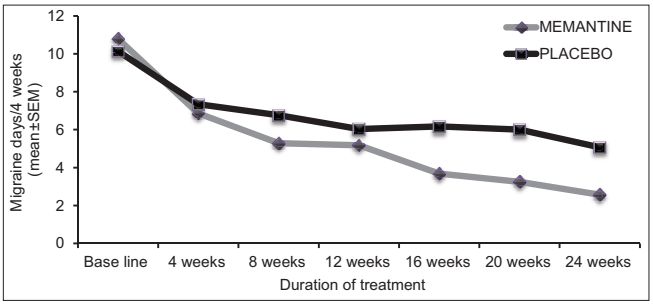

Figure 2: Effect of memantine on migraine frequency

50% responder rate

Most of the patients responded to memantine therapy well as evident by the 50% responder rate. The 50% responder rate among the memantine-receiving patients (85.7%) was significantly higher ($P = 0.005$) than placebo-receiving patients (51.7%) [Table 2 and Figure 3].

Rescue medication use during treatment of migraine with memantine

To evaluate the efficacy of memantine, we also analyzed use of rescue medication by migraine patients (3–12 migraine days/month) after the initiation of treatment with memantine [Table 3 and Figure 4]. The rescue medication intake reduced significantly in the patients receiving memantine as compared to the placebo-receiving patients starting from week 8 of the treatment (memantine: 3.14 [±0.34], placebo: 5.52 [±0.48], $P = 0.0001$). By week 24, significantly less ($P = 0.0001$) rescue medication use was reported by patients received memantine (0.75 [±0.23]) as compared to patients receiving placebo (3.72 [±0.63]). In addition, as compared to baseline, rescue medication use was decreased in both memantine (baseline: 8.79 [±0.47], week 24: 0.75 [±0.23]) and placebo-receiving patients (baseline: 9.17 [±0.35], week 24: 3.72 [±0.63]). However, the memantine-receiving patients used less rescue medication at week 24 of treatment than placebo-receiving patients by week 24.

Adverse events

Only a few adverse events were reported by the patients during the study [Table 4]. Most commonly fatigue, anorexia, dizziness, and nausea were reported. Similar adverse events were observed between memantine and placebo groups. No severe adverse events or death occurred during the study. Taken together, memantine appeared to be safe and well tolerated among patients with migraine.

Discussion

In this clinical study, we evaluated the efficacy and safety of memantine in migraine patients. We enrolled 60 adult patients

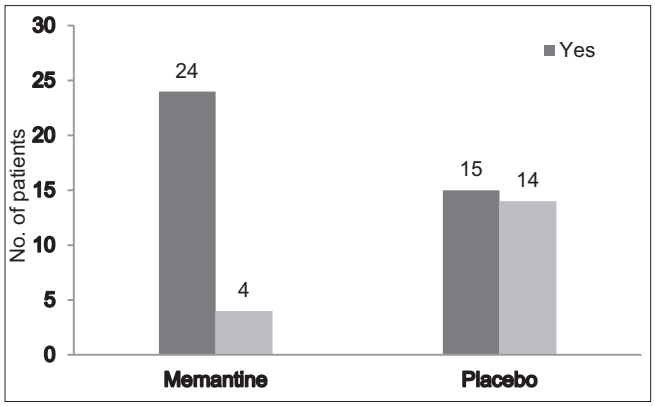

Figure 3: The 50% responder rate to memantine therapy

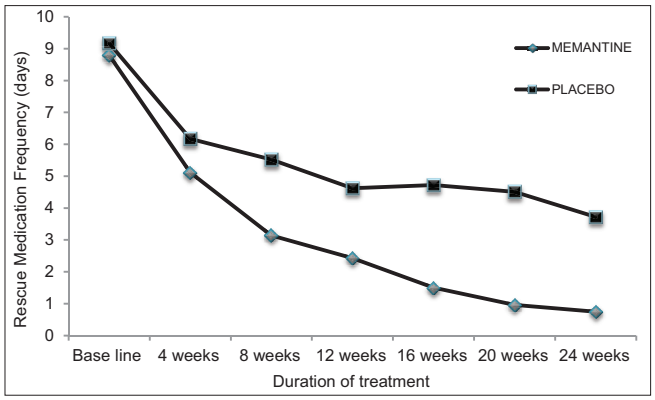

Figure 4: Rescue medication use during treatment of migraine with memantine

Table 1: Effect of memantine on migraine frequency (mean±standard error of mean)

Duration of treatment	Memantine	Placebo	*T*	*P*
Baseline	10.79±0.40	10.14±0.37	1.190	0.239
4 weeks	6.86±0.45	7.34±0.49	−0.730	0.469
8 weeks	5.29±0.42	6.76±0.53	−2.152	0.036
12 weeks	5.18±0.51	6.03±0.68	−0.999	0.322
16 weeks	3.68±0.38	6.17±0.48	−4.246	0.0001
20 weeks	3.25±0.44	6.00±0.69	−3.373	0.001
24 weeks	2.57±0.38	5.07±0.69	−3.174	0.003

Table 2: The 50% responder rate

Group	50% responder rate		χ^2	*P*
	Yes (%)	No (%)		
Memantine	24 (85.7)	4 (14.3)	7.62	0.005
Placebo	15 (51.7)	14 (58.3)		

Table 3: Rescue medication use during treatment of migraine with memantine

Duration of treatment	Memantine	Placebo	*T*	*P*
Baseline	8.79±0.47	9.17±0.35	−0.663	0.510
4 weeks	5.11±0.43	6.17±0.53	−1.570	0.122
8 weeks	3.14±0.34	5.52±0.48	−4.036	0.0001
12 weeks	2.43±0.34	4.62±0.65	−2.985	0.0001
16 weeks	1.50±0.23	4.72±0.53	−5.574	0.0001
20 weeks	0.96±0.26	4.51±0.69	−4.815	0.0001
24 weeks	0.75±0.23	3.72±0.63	−4.430	0.0001

Table 4: Adverse events

Adverse event	Memantine (*n*=28)	Placebo (*n*=29)
Fatigue	1	2
Anorexia	1	0
Dizziness	2	1
Nausea	1	2

with migraine (3–12 episodes per month for at least 6 months) in this study. Memantine at the dose of 10 mg/day showed significant reduction in primary efficacy measure of migraine frequency from the 16th week onward, when compared to placebo and this effect was maintained till the end of the study. It was also associated with significant improvements in several other efficacy measure including the 50% responder rate and rescue medication days every month. The adverse effects were mild and reported in <10% of patients. None of the patients discontinued treatment due to side effects.

A few clinical studies evaluated the efficacy of memantine for migraine patients. The retrospective study by Charles *et al*. analyzed 60 patients. They reported a reduction in headache frequency from 15.2/month to 6.1/month.[13] Another study by Bigal *et al*. reported a decrease in headache frequency from 21.5 at baseline to 14.3 days/month in 20 patients.[14] Krusz *et al*. reported a decrease in migraine frequency to 4.1 migraines per month or almost 56% less than at baseline, in 14 of 20 patients.[15] In comparison, we observed a significant reduction in the migraine frequency from 10.7/month to 2.3/month. However, a study by Charles *et al*. was a retrospective study, while Bigal *et al*. enrolled only refractive migraine patients and Krusz *et al*. included only chronic migraine patients. These studies were not placebo-controlled and previous migraine medications were not stopped. In contrast, we enrolled 60 patients and previous migraine medications were stopped before the commencement of our study. In addition, none of these studies evaluated the rescue medications intake frequency and the 50% responder rate, which we recorded and analyzed in this study.

Numerous studies assessed the efficacy of other drugs for migraine. However, they were conducted before the IHS criteria for migraine came into effect. Hence, it is difficult to compare results from recent studies with earlier studies. Few of the earlier studies used a headache index or score as primary end-point to assess efficacy of the interventional drug in migraine prevention.[16,17] Nonetheless, in our study, we used other migraine parameters as well to evaluate efficacy

of memantine. Hence, results from our study can be compared to earlier studies as well using the 50% responder rate. Divalproex produced the 50% responder rate of 48%, 44%, and 41% in earlier clinical studies, while gabapentin showed the 50% responder rate of 36%, amitriptyline showed the 50% responder rate of 50% and topiramate showed the 50% responder rate of 54%. Of note, responder rate in our study was observed at 87%, which was higher than any of other abovementioned therapeutic agents for migraine.

In this study, we observed a few adverse events, which were mild. Only eight patients had mild adverse events including fatigue, dizziness, anorexia, somnolence, and nausea. The most common side effects were dizziness followed by somnolence. These adverse events were expected for drugs of this class and would not prevent the use of memantine in the patients requiring preventive migraine treatment. Slow upward titration starting at 5 mg and increased up to 10 mg may enhance tolerability for memantine and help to avoid many of the adverse events reported. Of note, adverse events were transient and could be managed easily.

There were few limitations in our study. Our study had a short duration of treatment. In addition, this study enrolled a smaller number of patients. Hence, a large and long-term study is required to assess the long-term safety and efficacy of memantine in migraine patients. We observed that memantine is useful in migraine patients with 3–12 episodes/month. However, we have not included patients with chronic migraine, monthly frequency of ≥15 migraines, cluster migraine, trigeminal autonomic cephalalgias such as paroxysmal hemicranias and Short lasting Unilateral Neuralgiform Headache with Conjunctival injection and Tearing (SUNCT), and tension-type headache. Hence, additional studies are required to examine efficacy and safety of memantine in such patient populations. Moreover, efficacy of memantine when used in combination with other antimigraine drugs such as propranolol, flunarizine, and divalproex sodium also needs to be assessed. Finally, efficacy and safety of lower (5 mg) and higher (20 mg) doses of memantine should be addressed through systematic clinical trials.

Our study raised few important issues, which require further investigation. We observed that memantine is useful for episodic excitotoxicity disorder such as migraine. Will it be useful in other neurological disorders involving brain excitotoxicity such as motor neuron disease as well? Moreover, it will be useful to investigate the efficacy of other antiglutamate drugs in migraine since our study indicated that antiglutamate drug memantine is useful for migraine patients. In summary, this randomized, double-blind, placebo-controlled study showed that memantine (10 mg oral, once daily) significantly decreased the headache frequency and rescue medication intake in migraine patients as compared to placebo in migraine patients. It is well tolerated with a few mild adverse effects in migraine patients.

Conclusion

Memantine (10 mg) significantly decreases headache frequency and mean rescue medication intake. It is safe as adverse effects are few and mild.

Financial support and sponsorship

This study was financially supported by SRM Medical College & Research Centre, Kattankulathur.

Conflicts of interest

There are no conflicts of interest.

References

1. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. JAMA 1992;267:64-9.
2. Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population – a prevalence study. J Clin Epidemiol 1991;44:1147-57.
3. Neurology Channel. Migraine Headaches. Available from: http://www.neurologychannel.com/migraine/index.shtml [Last accessed on 2017 May 20].
4. Medical News Today. Targeting Glutamate Receptors for Migraine Prevention. Available from: http://www.medicalnewstoday.com/articles/148137.php.
5. Moskowitz MA, Nozaki K, Kraig RP. Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms. J Neurosci 1993;13:1167-77.
6. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA, *et al.* Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med 2002;8:136-42.
7. Kunkler PE, Kraig RP. Hippocampal spreading depression bilaterally activates the caudal trigeminal nucleus in rodents. Hippocampus 2003;13:835-44.
8. Afridi SK, Matharu MS, Lee L, Kaube H, Friston KJ, Frackowiak RS, *et al.* A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. Brain 2005;128:932-9.
9. Smith JM, Bradley DP, James MF, Huang CL. Physiological studies of cortical spreading depression. Biol Rev Camb Philos Soc 2006;81:457-81.
10. Obrenovitch TP, Zilkha E. High extracellular potassium, and not extracellular glutamate, is required for the propagation of spreading depression. J Neurophysiol 1995;73:2107-14.
11. Smith TR, Stoneman J, Munson P. Memantine for the prophylaxis of migraine: A report of 3 cases and discussion of pharmacology. Headache 2005;16:167-70.
12. Lacy CF, Armstrong LL, Goldman MP, Lance LL. Drug Information Handbook. 17th ed. Hudson, OH: Lexi-Comp; 2008. p. 123-54.
13. Charles A, Flippen C, Romero Reyes M, Brennan KC. Memantine for prevention of migraine: A retrospective study of 60 cases. J Headache Pain 2007;8:248-50.
14. Bigal M, Rapoport A, Sheftell F, Tepper D, Tepper S. Memantine in the preventive treatment of refractory migraine. Headache 2008;48:1337-42.
15. Krusz JC, Robert T. Preventing Chronic THH and Migraine with Namenda. Available from: http://www.headaches.about.com/od/medsarticlesandinfo/a/namenda_prev.htm. [Last accessed on 2017 May 20].
16. Diamond S, Medina JL. Double blind study of propranolol for migraine prophylaxis. Headache 1976;16:24-7.
17. Ziegler DK, Hurwitz A, Hassanein RS, Kodanaz HA, Preskorn SH, Mason J, *et al.* Migraine prophylaxis. A comparison of propranolol and amitriptyline. Arch Neurol 1987;44:486-9.