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Original Article

Pharmacology Section

Atorvastatin as an Add-on Therapy in Episodic Migraine Prophylaxis: A Randomised Controlled Study

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ABSTRACT

Introduction: Migraine is a primary headache disorder with an estimated frequency of 12% in the world population, ranked fifth among causes of disability worldwide in both sexes under 50 years. Conventional prophylactic agents are limited by adverse effects and poor tolerability. Atorvastatin, a HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitor with pleiotropic anti-inflammatory and endothelial-protective properties, has been proposed as a potential prophylactic agent in migraine.

Aim: To assess the efficacy and tolerability of Atorvastatin 20 mg/day as add-on therapy on frequency, intensity and duration of migraine attacks over a 3-month treatment period compared with standard therapy alone.

Materials and Methods: The present prospective, parallel group, open-labelled, randomised controlled study was conducted at the Outpatient Department of Neurology, Government Kilpauk Medical College and Hospital, Chennai, Tamil Nadu, India, over eight months from November 2020 to June 2021. A total of 63 participants with episodic migraine (4-15 attacks/month for ≥1 year) were randomised into a control group (n=32, standard prophylaxis alone) and an atorvastatin group (n=31, standard prophylaxis + Atorvastatin 20 mg Once Daily (OD) for 3 months). Primary outcome was ≥50% responder rate in frequency of attacks at end of treatment. Secondary outcomes included 50% responder rate in pain intensity (Numerical Rating Scale) and mean headache duration. Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 28. A p-value of <0.05 was considered statistically significant.

Results: The mean age of participants was 39.65±8.56 years in Atorvastatin group and 40.06±8.61 years in Control group. Out of 63 participants 56 (88.9%) were female. At the end of the third month, 50% responder rate in frequency of attacks was 58.06% in Atorvastatin group vs 18.75% in the control group (p<0.001). Mean frequency of attacks declined significantly from baseline 5.77±1.18 to 2.58±1.09 in the Atorvastatin group versus 5.81±1.12 to 3.75±1.22 in the control group (p<0.001). Significant reduction was also observed in pain intensity (p=0.004) and headache duration (p<0.001) at the end of the third month. No serious adverse events were reported; statin-induced myalgia was the most common Adverse Drug Reaction (12.9%).

Conclusion: Atorvastatin 20 mg/day as add-on therapy significantly reduces the frequency, intensity and duration of migraine attacks with good tolerability. It offers added cardiovascular protection in a population at elevated vascular risk, making it a promising option for migraine prophylaxis.

Keywords: Combination, Drug therapy, Headache disorders, Hydroxymethylglutaryl-coenzyme a reductase inhibitors, Migraine disorders

INTRODUCTION

Migraine is a primary headache disorder with an estimated frequency of 12% in the world population [1]. The Global Burden of Diseases study 2019 ranked it the fifth highest cause of disability worldwide in both sexes under the age of 50 years [2]. The one-year prevalence is 6% in men and 18% in women, with peak prevalence in the fourth decade [3]. Migraine causes substantial pain and disability affecting physical, emotional and social quality of life. There is a strong genetic predisposition, with first-degree relatives two to four times more likely to develop migraine than the general population [4].

Pathogenesis involves activation of the trigeminovascular system, Cortical Spreading Depolarisation (CSD), and the release of vasoactive neuropeptides such as Calcitonin Gene-Related Peptide (CGRP). CSD transiently opens neuronal channels releasing inflammatory mediators including nitric oxide and prostanoids, activating and sensitising perivascular trigeminal primary afferents that transmit nociceptive impulses [5].

Pharmacotherapy forms the mainstay of treatment, comprising acute and preventive medications [6]. Commonly used prophylactic agents are sodium valproate, propranolol, and amitriptyline. Though they are proven agents their use is limited by adverse effects including weight gain, somnolence, cognitive slowing, and hypotension, resulting in poor adherence [7]. Novel monoclonal antibodies against CGRP (e.g., Erenumab) are approved for episodic and chronic migraine but remain prohibitively costly and restricted in availability [8].

Migraineurs are at increased risk for vascular events including stroke, myocardial infarction, peripheral arterial disease and cardiovascular mortality, with many of these events preceded by endothelial dysfunction [9,10]. Statins, particularly Atorvastatin, are established cardioprotective agents that improve endothelial dysfunction, reduce vascular wall inflammation, decrease platelet aggregation and attenuate oxidative stress-mechanisms that may also be relevant to migraine pathophysiology [11]. Studies specifically evaluating statins in migraine prophylaxis remain limited. Buettner C et al., studied Simvastatin 20 mg/day in combination with Vitamin D for migraine prevention but did not demonstrate significant reduction in pain intensity or duration [12]. Hesami O et al., conducted a randomised trial comparing Atorvastatin 20 mg/day against sodium valproate in episodic migraine, demonstrating reduction in frequency and intensity of attacks [13]. However, data on Atorvastatin as an add-on therapy to conventional standard prophylaxis in episodic migraine is scarce in Indian population. Hence, the present study was designed to assess the efficacy and tolerability of Atorvastatin as add-on therapy for migraine prophylaxis.

MATERIALS AND METHODS

The present study was a prospective, parallel group, open-labelled, randomised controlled study registered in Clinical Trial Registry of India (CTRI/2021/04/032998) conducted at the Outpatient Department of Neurology, Government Kilpauk Medical College and Hospital, Chennai, Tamil Nadu, India, from November 2020 to June 2021 (eight months). The study was approved by the Institutional Ethics Committee of Government Kilpauk Medical College (Protocol ID 402/2020, Meeting held on 12/11/2020) and conducted in accordance with Indian Council of Medical Research (ICMR) guidelines on biomedical research and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all the participants prior to enrolment.

Inclusion and Exclusion Criteria: Patients aged 18-50 years of both sexes, diagnosed with episodic migraine as per the International Headache Society (ICHD-3) criteria [14], on prophylactic medication for at least one year, and with 4-15 migraine attacks per month in the preceding two months were enrolled. Patients with chronic daily headache (≥15 days/month), those already on statins or any lipid-lowering agents, patients with renal disease, elevated creatinine kinase (>3× Upper Limit of Normal (ULN)), elevated transaminases (Aspartate Aminotransferase (AST)/Alanine Aminotransferase (ALT) >2× ULN), pregnant or nursing women, those with uncontrolled diabetes mellitus, thyroid disease, psychiatric illness, known hypersensitivity to statins, and those with a history of drug or substance abuse were excluded.

Sample size calculation: Sample size was calculated using Open Epi software. Based on the outcome of the study by Buettner C et al., a sample size of 32 per group (total 64) was calculated to detect a difference of 26% in 50% reduction in frequency of attacks with 80% power and 95% confidence level [12].

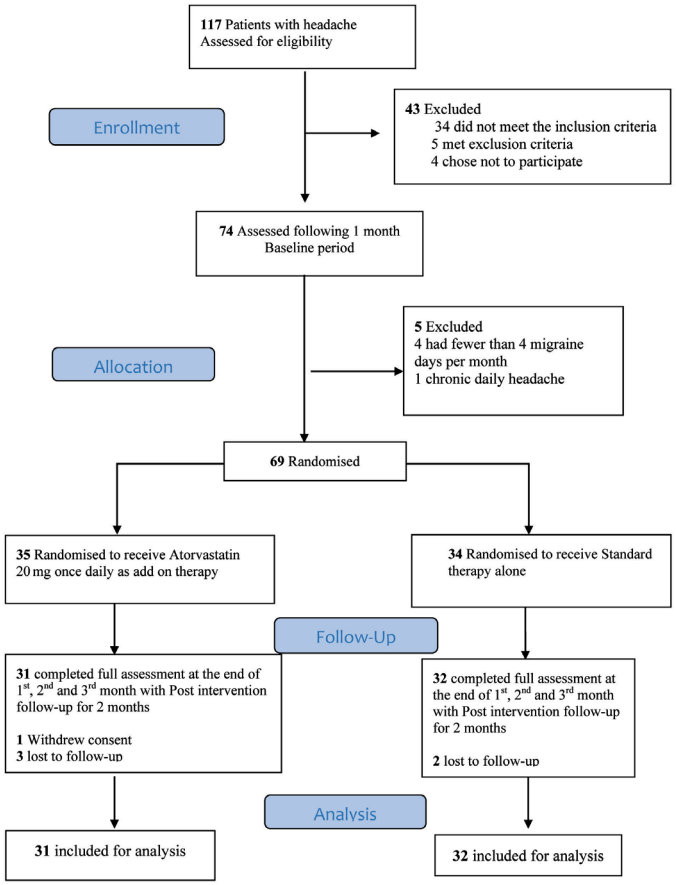
After screening 117 patients, 74 fulfilled inclusion criteria. Following a one-month baseline period (during which migraine calendars were maintained), four patients with <4 episodes/month and one with chronic daily headache were excluded. Sixty-nine patients were randomised using a computer random number generator into two groups: Control group (n=34, standard prophylaxis alone) and Atorvastatin group (n=35, standard prophylaxis + Tab. Atorvastatin 20 mg OD at night after food). The study comprised a 3-month drug period followed by a 2-month follow-up period. Six patients dropped out (four from Atorvastatin group: three lost to follow-up, one withdrew consent; two from control group: lost to follow-up). Final analysis included 63 participants (31 Atorvastatin, 32 Control). Standard prophylaxis consisted of Tab. Amitriptyline 25 mg/day at night and/or Tab. Propranolol 40 mg twice a day (BID) [Table/Fig-1].

Study Procedure

At each monthly visit, empty tablet strips and migraine calendars were collected, and medication was reissued. Participants were enquired about adverse effects at each visit; all Adverse Drug Reactions (ADRs) were documented, causality assessed using the World Health Organization - Uppsala Monitoring Centre (WHO-UMC) scale [15] and reported to the Regional Pharmacovigilance Centre using the Pharmacovigilance Programme of India (PvPI) Suspected ADR reporting form.

After completion of 3-month intervention period, participants continued only the standard prophylactic therapy and were followed up for an additional two months to assess for any rebound increase in migraine episodes.

Outcome measures: Primary outcome was ≥50% responder rate in frequency of attacks at end of the third month. Secondary outcomes included: (1) ≥50% responder rate in pain intensity by Numerical Rating Scale (NRS; 0-10); (2) mean duration of headache per episode; and (3) change in associated symptoms (nausea, vomiting, photophobia, phonophobia).



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) chart of the study.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 28. Qualitative variables were reported as frequency and percentage. Quantitative variables were reported as mean±Standard Deviation (SD). Intergroup comparisons were performed using Student's t-test. The 50% responder rate was compared using Chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

Of 117 patients screened, 69 were randomised (35 Atorvastatin, 34 Control). A total of 6 patients dropped out (four from Atorvastatin group: three lost to follow-up, one withdrew consent; two from control group: lost to follow-up). Final analysis included 63 participants (31 Atorvastatin, 32 Control). Baseline characteristics of both groups are shown in [Table/Fig-2]. There were no statistically significant differences in baseline characteristics between the two groups.

Parameters	Atorvastatin group (n=31)	Control group (n=32)	p-value
Age (years), Mean±SD	39.65±8.56	40.06±8.61	0.848
Female, n (%)	27 (87.1%)	29 (90.6%)	-
Duration of disease (years), Mean±SD	5.23±2.36	4.59±2.59	0.316
Frequency of attacks/month, Mean±SD	5.77±1.18	5.81±1.12	0.895
NRS pain score, Mean±SD	6.16±1.24	6.34±1.07	0.533
Duration of headache (hours), Mean±SD	11.13±2.43	11.50±2.11	0.520
On Amitriptyline and/or Propranolol	18	20	-
On both Amitriptyline and Propranolol	13	12	-

[Table/Fig-2]: Baseline characteristics of participants N=63.
NRS-Numeric Rating Scale

Primary Outcome

50% responder rate in frequency of attacks: At end of the third month, 18/31 (58.06%) participants in the Atorvastatin group achieved ≥50% reduction in frequency of attacks compared with

6/32 (18.75%) in the Control group (p<0.001). The intergroup comparison across months is shown in [Table/Fig-3].

Time period	Atorvastatin group n (%)	Control group n (%)	p-value
1st month	4 (12.9%)	2 (6.25%)	0.368
2nd month	13 (41.94%)	2 (6.25%)	<0.001
3rd month	18 (58.06%)	6 (18.75%)	<0.001

[Table/Fig-3]: Intergroup analysis of ≥50% responder rate in frequency of attacks using Chi-square test.

Mean frequency of attacks: In the Atorvastatin group, mean frequency declined from 5.77±1.18 (baseline) to 5.00±1.67 (1st month), 3.19±0.95 (2nd month), and 2.58±1.09 (3rd month). In the Control group, mean frequency declined from 5.81±1.12 to 5.16±1.11, 4.22±1.01, and 3.75±1.22, respectively. Intergroup comparison showed significant difference at end of 2nd and 3rd months (p<0.001), but not at end of 1st month (p=0.663). [Table/Fig-4] shows the detailed comparison.

Time period	Atorvastatin group (Mean±SD)	Control group (Mean±SD)	p-value
Baseline	5.77±1.18	5.81±1.12	0.895
1st month	5.00±1.67	5.16±1.11	0.663
2nd month	3.19±0.95	4.22±1.01	<0.001
3rd month	2.58±1.09	3.75±1.22	<0.001

[Table/Fig-4]: Comparison of mean frequency of attacks between the groups using Student's t-test.

Secondary Outcomes

Pain intensity (NRS Score): The 50% responder rate in pain intensity at end of 3rd month was 48.39% in the Atorvastatin group vs 21.88% in the control group (p=0.019). [Table/Fig-5] shows the detailed comparison.

Time period	Atorvastatin group n (%)	Control group n (%)	p-value
1st month	3 (9.68%)	1 (3.13%)	0.742
2nd month	11 (35.48%)	4 (12.5%)	0.040
3rd month	15 (48.39%)	7 (21.88%)	0.019

[Table/Fig-5]: Comparison of pain intensity (NRS score) between the groups using Chi-square test.

Mean NRS pain score in the Atorvastatin group reduced from 6.16±1.24 to 3.29±1.16 at 3rd month vs 6.34±1.07 to 4.34±1.56 in the control group; intergroup difference was significant at 2nd and 3rd months (p=0.001 and p=0.004, respectively) [Table/Fig-6].

Time period	NRS score - Atorvastatin (Mean±SD)	NRS score - Control (Mean±SD)	p-value
Baseline	6.16±1.24	6.34±1.07	0.533
1st month	5.39±1.59	5.84±1.29	0.215
2nd month	3.84±1.28	4.94±1.32	0.001
3rd month	3.29±1.16	4.34±1.56	0.004

[Table/Fig-6]: Comparison of mean NRS pain score between the groups using Student's t-test.

Duration of headache: Mean headache duration per episode in the Atorvastatin group reduced from 11.13±2.43 hours to 4.77±1.84 hours at 3rd month, compared with 11.50±2.11 to 7.19±1.96 hours in the Control group (p<0.001). No significant difference was noted at the end of 1st month (p=0.395) [Table/Fig-7].

Time period	Duration (h) - Atorvastatin (Mean±SD)	Duration (h) - Control (Mean±SD)	p-value
Baseline	11.13±2.43	11.50±2.11	0.520
1st month	9.68±3.28	10.28±2.23	0.395
2nd month	6.35±1.87	8.25±1.74	<0.001
3rd month	4.77±1.84	7.19±1.96	<0.001

[Table/Fig-7]: Comparison of mean duration of headache between the groups using Student's t-test.

Associated symptoms: At the end of the 3rd month, statistically significant reduction in nausea (p=0.03), photophobia (p<0.001), and phonophobia (p=0.002) was observed in the Atorvastatin group compared with the control group. No significant difference was observed in vomiting between the two groups (p=0.67) [Table/Fig-8].

Symptoms	Atorvastatin 3rd month, n (%)	Control 3rd month, n (%)	Atorvastatin Baseline n (%)	Control Baseline n (%)	p-value (3rd month)
Nausea	10 (32.26%)	19 (59.37%)	24 (77.41%)	23(71.87%)	0.030
Vomiting	2 (6.45%)	3 (9.37%)	6 (19.35%)	5 (15.62%)	0.670
Photophobia	7 (22.58%)	20 (62.5%)	21 (67.74%)	22 (68.75%)	<0.001
Phonophobia	6 (19.35%)	18 (56.25%)	19 (61.29%)	20 (62.5%)	0.002

[Table/Fig-8]: Associated symptoms at 3rd month - intergroup comparison using Chi-square test.

Follow-up (5th Month)

Two months after cessation of Atorvastatin, the mean frequency of attacks in the Atorvastatin group increased slightly from 2.58 (3rd month) to 2.81±1.05 (5th month) but remained significantly lower than the Control group (3.50±1.29; p=0.02). Mean NRS pain score in the Atorvastatin group rose marginally to 3.65±1.17 from 3.29 at end of treatment, which was not significantly different from the control group (3.75±1.05; p=0.7). The intergroup comparison at the end of 3rd and 5th month is shown in [Table/Fig-9].

Parameters / Period	Atorvastatin (Mean±SD)	Control (Mean±SD)	p-value
Mean frequency of attack 3rdmonth/5th month	2.58±1.09/ 2.81±1.05	3.75±1.22/ 3.50±1.29	<0.001 / 0.02
Mean NRS pain score 3rd month/5th month	3.29±1.16/ 3.65±1.17	4.34±1.56/ 3.75±1.05	0.004 / 0.70

[Table/Fig-9]: Comparison of mean frequency of attacks and the mean value of NRS score at 3rd and 5th month between the groups using Student's t-test.

Adverse Drug Reactions

In the Atorvastatin group, 5/31 (16.1%) participants developed mild-to-moderate ADRs. Statin-induced myalgia was the most common ADR (4 patients, 12.9%), followed by flu-like symptoms (3 patients, 9.6%), Gastrointestinal (GI) complaints (3 patients, 9.6%), and difficulty in sleeping (1 patient, 3.2%). All ADRs were managed symptomatically. No serious adverse events were reported during the study period [Table/Fig-10].

Adverse events	Atorvastatin group (n=31)	WHO-UMC causality
Myalgia	4 (12.9%)	Probable
Flu-like symptoms	3 (9.6%)	Possible
GI complaints	3 (9.6%)	Probable
Difficulty in sleeping	1 (3.2%)	Possible

[Table/Fig-10]: Summary of Treatment emergent adverse events in Atorvastatin group with WHO-UMC causality assessment.

DISCUSSION

In the present prospective, open-labelled, randomised controlled study, the effect of Atorvastatin 20 mg co-administered with standard treatment on decreasing the number of migraine attacks and pain intensity was assessed. Median age of the participants in both groups was approximately 39-40 years, consistent with migraine being most prevalent in the fourth decade, as reported by Bigal ME et al., [16]. Majority of participants were female (88.9%),

similar to the Indian community-based study by Ray BK et al., that reported a female prevalence of 81.87% [17].

The primary outcome 50% responder rate in frequency of attacks-was 58.06% in the Atorvastatin group and 18.75% in the Control group at end of 3rd month (p<0.001). This is comparable to the triple-blinded RCT by Ganji R et al., where addition of Atorvastatin to a preventive regimen achieved a responder rate of 65% [18]. The effect size of the primary outcome in the present study was 39%. As per the Cochrane systematic review on topiramate by Linde M et al., a 30% reduction in migraine attacks exceeds the threshold considered clinically significant for migraine prophylaxis [19]. The 50% responder rate for frequency in the current study is comparable to published rates for propranolol, amitriptyline, and sodium valproate [20,21].

The 50% responder rate in pain intensity at end of 3rd month was 48.39% in the Atorvastatin group vs 21.88% in the Control group (p=0.019). This is consistent with the double-blind RCT by Hesami O et al., which reported 45.7% of participants in the Atorvastatin group achieving >50% pain reduction. In studying headache duration, there was a significant reduction from 11.13 hours at baseline to 4.77 hours at 3rd month in the Atorvastatin group [13]. Buettner C et al., reported no significant reduction in pain intensity and duration with Simvastatin [12], a discrepancy likely attributable to the relatively lower pharmacological efficacy of Simvastatin compared with Atorvastatin [22], which may translate to a lesser pleiotropic effect, or cultural influences on pain reporting [23].

Studies have reported a higher prevalence of cardiovascular and cerebrovascular disorders among migraineurs. A large prospective cohort study by Kurth T et al., and a meta-analysis of 16 cohort studies by Mahmoud AN et al., verified the association between migraine and cardiovascular disease [24,25]. Statins could thus offer a dual benefit in this high-risk population, namely migraine prophylaxis and reduction of cardiovascular mortality.

Tolerability was excellent with no serious adverse events. This contrasts with other commonly used prophylactic agents, which have higher rates of unintentional effects resulting in poor long-term adherence, as documented in the systematic review by Hepp Z et al., [26]. A relevant consideration in the Indian context, where India accounts for a disproportionately high burden of diabetes [27], is the known diabetogenic potential of statins. As per American Academy of Family Physicians (AAFP) guidelines [28], comorbid conditions should guide prophylactic agent selection; statins may be tapered after 12 months of headache control, or continued in those with concurrent cardiovascular risk, where the cardiovascular benefit outweighs the small increase in fasting blood glucose.

Limitation(s)

The association with vitamin D levels could not be evaluated in this study as vitamin D assays were not available at the study site. Other limitations of the present study include the open-label design (subjective outcome measures necessitate double-blinding and placebo control), small sample size, short duration, and lack of data on abortive medication use as a secondary outcome variable.

CONCLUSION(S)

Atorvastatin 20 mg/day as add-on therapy to standard prophylaxis significantly reduces the frequency, intensity, and duration of migraine attacks with good tolerability and adherence. With the added benefit of cardiovascular protection in a population at elevated cardiovascular risk, Atorvastatin is a promising alternative in the prophylaxis of episodic migraine. Larger, double-blind, placebo-controlled trials incorporating vitamin D level monitoring and one-on-one comparative arms are recommended to further establish its role.

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- For any images presented appropriate consent has been obtained from the subjects. NA

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