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Original Research Article

Efficacy of Amitriptyline in Migraine Prophylaxis: A Comparative Study of Two Different Doses of Amitriptyline

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ABSTRACT

Background and objectives: Amitriptyline in varying dosages from 10 mg to 50 mg has been used effectively in prophylaxis of Migraine. No reliable evidence in the form of a comparative study is available regarding efficacy of a lower dose of Amitriptyline for prophylactic therapy. Hence, this study was undertaken to compare the efficacy of Amitriptyline at a lower dose of 5 mg against a standard dose of 10 mg in achieving control of Migraine symptoms.
Materials and methods: This was a comparative, double-blinded, randomized controlled study with 82 patients with Migraine requiring prophylaxis. Subjects were allocated into two groups, with 41 patients in each receiving Amitriptyline 10 mg and 5 mg respectively, as once daily regimen per orally for three months. Improvement in Headache severity (0-10 numeric pain rating scale) and Migraine symptoms (9-point scale) was noted at follow-up.
Results: Both groups showed significant improvement in headache and symptom scores through three months of follow-up (p-value < 0.0001, ANOVA). The improvement in the scores among patients in group A was significantly more than observed in group B. No significant adverse events were noted.
Conclusion: Amitriptyline may be used with significant benefit in the prophylaxis of Migraine. Amitriptyline at a dose of 10 mg is more efficacious than that at 5 mg in controlling headache and the associated symptoms of Migraine. A minimum dose of 10 mg may be safely used without any increased risk of adverse effects.

Key words: Migraine, Tricyclic antidepressants, Amitriptyline, headache, prophylaxis

INTRODUCTION

Migraine is a common cause of primary headache, ranked as the third most prevalent disorder and seventh most common specific cause of disability worldwide,[1] according to Global Burden of Disease Survey, 2010.[2] This underlines the enormity of the socio-economic burden posed by migraine on the global population. Migraine is basically of two types- either without or with aura. Cortical spreading depression has been implicated in

development of migraine with aura, while blood flow changes in brainstem and cortical changes secondary to pain activation have been observed in migraine without aura. Although migraine is primarily a vascular disorder, the involvement of sensitization of pain pathways and role of messenger molecules such as Nitric Oxide (NO), 5-hydroxytryptamine (5-HT) and Calcitonin gene-related peptide (CGRP) have been recognized.[3] Migraine can be debilitating if adequate control of their symptoms is not achieved. Initial treatment is directed at lifestyle changes, avoidance of stress/trigger factors and abortive medications. Prophylaxis is initiated in whom these measures fail to control the frequency, duration or severity of symptoms.[4] A variety of drugs with an equally varied efficacy and safety profiles have been found useful in the prevention of migraine headache. Most of these drugs act by either inhibition of cortical spreading depression or by restoration of nociceptive inhibition.[5] The association of migraine with depression, anxiety, phobias and anxiety disorders has been confirmed by various studies. A higher risk of depression in migraine sufferers than in non-migraine patients has been reported.[6] Amitriptyline is the only antidepressant with high quality evidence of efficacy in migraine prophylaxis. Its effects are attributed to the enhanced opioid receptor actions, decrease of serotonin receptors and up-regulation of norepinephrine at synapses. However, there is no consensus on the lowest effective dose of Amitriptyline while it has been widely used in doses ranging from 10mg to 50mg.[7]

Several drugs with proven efficacy in prevention of migraine are available. The choice of drug therapy for long term prophylaxis for migraine should take the risk-benefit ratio, co-morbidities in the patient, compliance and cost of the treatment into consideration. The drug with the potential of highest benefit and lowest risk to the patient should be chosen. Equally important should be the choice of the lowest effective dosage of the drug, which must further minimize the adverse effects of the drug. Few studies have evaluated the efficacy of Amitriptyline at lower doses (5mg) with mixed results. No reliable evidence in the form of a comparative study is available regarding efficacy of a lower dose of Amitriptyline for prophylactic therapy. Hence, this study was designed to compare the efficacy of oral Amitriptyline at a lower dose of 5mg against the standard dose of 10mg, as once daily prophylactic therapy of migraine headache and its associated symptoms.

MATERIALS AND METHODS

Study type: This was a phase IV, double-blinded randomized controlled, comparative clinical trial with a parallel group design (non-inferiorty).

Study settings: Department of ENT, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari (Dist), Tamil Nadu. This study was ethically cleared by Institutional Human Ethical Committee.

Ethical clearance: Ethical clearance for this study was obtained from the Institutional Human Ethics Committee, Sree Mookambika Institute of Medical Sciences, Kulasekharam.

Inclusion criteria:

- Patients between 18 and 80 years of age, of either sex (male/female) with a diagnosis of Migraine either with or without aura as per International Headache Society (2013, 3rd edition)[3] definition of Migraine were recruited in the study.
- Patients had more than two attacks of headache per month, each episode lasting for more than two hours

and/or of such severity to cause substantial disability.

- Patients with headache that was refractory to abortive drug therapy or in whom such drugs were intolerable, contraindicated or overused (more than twice a week) were also included in the study.

Exclusion criteria:

- Patients with other known causes of headache in addition to migraine.
- Patients with known hypersensitivity to or contraindication to the use of Amitriptyline were excluded from the study.

Study design:

Group-A: Amitriptyline (10 mg/OD/ 3 months)

Group-B: Amitriptyline (5 mg/OD/3 months)

Procedure: Eighty two consecutive patients with Chronic Migraine who fulfilled the criteria for inclusion and exclusion were included in the study. Eligible patients were allocated into two groups based on a computer generated random number sequence by a neutral observer. Allocation concealment was effected by placing the random numbers printed on a slip of paper in sequentially numbered opaque sealed envelopes, which were opened only just before allocation of patients. Patients in group A (Positive Control group) received Tablet Amitriptyline 10 mg once daily, and those in group B (Study group) received Tablet Amitriptyline 5 mg once daily for three months. Headache severity scores (using 0-10 numeric pain rating scale) [8,9] of patients in both groups were noted at the beginning of therapy, and also at the end of first, second and third months. A score of '0' indicated complete relief, 1-3 corresponded to mild, 4-6 to moderate and 7-10 to severe headache. The overall improvement in migraine symptoms other than headache, including nausea, vomiting, photophobia, phonophobia, sleeplessness, anxiety and confusion,[10] at follow-up was assessed by Physician Global Assessment, Response to Treatment (PGART) 9-point Scale.[11] The patients and investigator who assessed the patients at recruitment and at follow-up were blinded to the treatment allocation. The results were thereafter compared and analyzed.

Statistical analysis:

The statistical analysis was done by using SPSS (20.0) version software. Two-factor repeated measures Analysis of variance (ANOVA) was done to find statistical significance in difference between the headache scores at recruitment through follow-up, between the two groups and also within each group. The same test was employed to assess the difference in the PGART scores at follow-up both within each group and between the groups. Fisher's exact test was applied to find statistically significant difference in the incidence of adverse effects, between the groups. P-value less than 0.05 ($P < 0.05$) was considered statistically significant at 95% confidence interval.

RESULTS

The study comprised of 82 patients in two groups, each with 41 patients. The ages of patients included ranged from 16 to 62 years. There were 17 males and 24 females in Group A. In Group B, there were 14 males and 27 females. The Headache scores of patients evaluated at presentation, first, second and third months were as shown in (Table-2). A significant improvement in the headache scores in both groups was noted at the end of three months (p value <0.0001, Table 4). In Group A, 80.5% patients presented with severe headache and the rest had moderate severity of headache. Among these patients, 17.1% had complete relief from headache, while

80.5% had only mild headache at the end of the study period. In Group B, 87.8% patients had severe headache at the beginning of the study and the remaining patients had headache of moderate severity. These patients reported a significant improvement in the headache with 65.9% and 34.1% patients having mild and moderate severity of headache respectively, at the end of three months. However, none of the patients in Group B had complete relief from headache. The improvement in the headache scores was thus better among those in Group A than in Group B, and this difference was statistically significant (p-value< 0.0001). PGART scores assessing the improvement in the overall control of symptoms associated with Migraine showed significant improvement through the follow-up period in both treatment groups (Table-3). Control of symptoms of Migraine was again found to be better among the patients in Group A (p-value < 0.001, Table-5). In Group A, 82.9% patients had marked improvement in the symptoms associated with Migraine, while 14.6% reported complete relief. Among those in Group B, marked improvement in Migraine symptoms was noted in 70.7% patients while 29.7% showed moderate improvement. Incidence of adverse effects among the two groups did not show statistically significant difference (two-tailed p value > 0.05, Table-6). Sedation was reported as a side effect by all patients in both groups. However, troublesome sedation significantly affecting the daily activities was observed in none of these patients. Mild epigastric distress was reported by three patients in Group A and one in Group B. Nausea was reported by one patient in Group A. The average weight gain among subjects in either group was 0.037 kg and 0.030 kg respectively.

Table-1: Physician Global Assessment, Response to Treatment 9-point (PGART) Scale.

Score	Improvement
+4	Complete clearance of signs and symptoms (about 100% improvement)
+3	Marked improvement (about 75% improvement)
+2	Moderate improvement (about 50% improvement)
+1	Slight improvement (about 25% improvement)
0	Unchanged
-1	Slight worsening (about 25% worse)
-2	Moderate worsening (about 50% worse)
-3	Marked worsening (about 75% worse)
-4	Very marked worsening (about 100% worse)

Table-2: Improvement in headache scores and severity, from presentation through the period of follow-up.

Treatment Group	Headache scores	Number of patients			
		At presentation	1 month	2 months	3 months
A	Nil	0	0	1	7
	Mild	0	9	33	33
	Moderate	8	29	7	1
	Severe	33	3	0	0
B	Nil	0	0	0	0
	Mild	0	1	9	27
	Moderate	5	27	30	14
	Severe	36	14	2	0

Table-3: Clinical improvement as determined by PGART scores in the treatment groups at follow-up.

Treatment group	Clinical improvement (PGART scores)	Number of patients		
		1month	2 months	3 months
A	Unchanged	0	0	0
	Slight	7	1	0
	Moderate	17	9	1
	Marked	17	31	34
	Complete	0	0	6
B	Unchanged	0	0	0
	Slight	14	5	0
	Moderate	20	22	12
	Marked	7	14	29
	Slight	0	0	0

Table-4: Comparison of treatment results among the two groups based on the changes in the headache scores from presentation to end of follow-up.

Treatment group	Mean Headache scores				p-value
	At presentation	1 month	2 months	3 months	
A	7.51	4.56	2.37	1.29	<0.0001
B	7.85	5.85	4.51	3.12	<0.0001

(*p-values calculated for comparison of headache scores before beginning of prophylaxis and through the follow-up visits (1st, 2nd and 3rd months) by repeated measures ANOVA. P-values < 0.05 were considered to be statistically significant)

Table-5: Comparison of treatment results among the two Groups based on the improvement in the PGART scores Through 1st, 2nd and 3rd months of follow-up.

Treatment group	Mean PGART scores			p-value
	1 month	2 months	3 months	
A	2.24	2.73	3.12	<0.0001
B	1.83	2.22	2.71	<0.0001

(*p-values were calculated for comparison of PGART scores through the follow-up visits (1st, 2nd and 3rd months) by repeated measures ANOVA. P-values < 0.05 were considered to be statistically significant).

Table-6: Comparison of adverse effects of Amitriptyline occurring anytime during follow-up.

Adverse effect	Number of patients		p-value
	Group A	Group B	
Sedation	41	41	> 0.05
Epigastric distress	3	1	> 0.05
Nausea	1	0	> 0.05

(*p-values were calculated for comparative incidence of adverse effects occurring during the period of study by Fisher's exact test. Two-tailed P-values < 0.05 were considered to be statistically significant)

DISCUSSION

Migraine is one of the most common disabling conditions globally, which poses a unique, significant burden on the quality of life according to Osterhaus JT et al. (1994).[12] Such disabling headaches often need acute pain medications. If the frequency, severity or duration of such headache episodes increases, prophylaxis may be indicated. Need for frequent acute pain medications also warrant prophylactic therapy. Amitriptyline is one of the frontline drugs [13-15] with a proven efficacy and acceptable levels of adverse drug effects. It is the most commonly used tricyclic antidepressant for headache prevention.[16] It produces a rapid response within four weeks when used for prophylaxis of migraine.[17] There is no consensus about the lowest effective dosage of Amitriptyline. Hence, this study was taken up with the objective of evaluating the efficacy of a lower dose of Amitriptyline (5 mg) in comparison with the more commonly used dosage of 10 mg, over a three months follow-up period. The period of follow-up adopted in this study conforms with the observation by Evers S et al.[18] that migraine prophylaxis may be considered successful if migraine attacks are reduced by atleast 50% in three months.

A comparison of Amitriptyline 25mg therapy with placebo by Couch JR et al.[19] reported a superior response to Amitriptyline, with improvement in frequency of headache of ≥ 50% at eight weeks (25% vs. 5%, p= 0.031) and at 16 weeks (46% vs. 9%, p=0.043). A controlled trial involving 100 patients determined that the difference between Amitriptyline and placebo response rates was significant (p<0.05).[20] Jackson JL et al. (2010) in their meta-analysis of 37 studies, observed that tricyclic antidepressants were more effective than selective serotonin re-uptake inhibitors in preventing migraine attacks, and that their effectiveness increased over time.[21] Levinstein B (1991) in a crossover study reported amitriptyline to be effective in 50%-60% of cases compared with propranolol and cyproheptadine.[22] An improvement in over 80% of cases of migraine was reported by Hershey et al. (2000) with amitriptyline.[23] Yet, the data on effectiveness of amitriptyline in the preventive treatment of migraine was found to be insufficient in a review of 166 articles concerning treatment of migraine, by Lewis D et al. (2004).[24]

This study comprised of 82 consecutive patients randomly assigned into two treatment groups A and B with 41

patients in each. Those in Group A received oral Amitriptyline 10 mg and those in Group B received oral Amitriptyline 5 mg for three months.

The Headache scores rated on a 0-10 numeric pain rating scale among patients in either groups showed significant improvement at the end of three months follow-up. However, those in the group A had greater control of their headache in terms of severity of attacks.

The overall improvement in the Migraine symptoms was rated as per Physician Global Assessment, Response to treatment 9-point scale (PGART scores). Significant relief from the symptoms associated with Migraine and improvement in the general feeling of well-being were observed in both groups. Patients in the Amitriptyline 10 mg group however, had better control of all the symptoms. This difference between the groups was observed to be statistically significant.

An open-label six months prospective study by Lampl C et al.[25] compared the prophylactic benefit of 50 mg of Amitriptyline with 25 mg of the same, in reducing the number of migraine days. The authors did not observe a statistically significant difference between the two groups at three and six months of follow-up.

Common adverse effects of Amitriptyline are sedation, dry mouth, metallic taste, epigastric distress and weight gain. Uncommon adverse effects of Amitriptyline include constipation, dizziness, mental confusion, tachycardia, palpitations, blurred vision, urinary retention, orthostatic hypotension.[26,27] The above adverse effects are usually tolerable as the dosage used for Migraine prophylaxis is low. Epigastric distress was observed in three subjects in Group A and one in Group B. One patient in Group A reported nausea. The adverse effects reported were transient in all the cases and subsided without treatment. None of these patients required discontinuation of Amitriptyline. All patients in either group reported sedation. It was observed to be desirable in all, as most of these patients had history of sleeplessness before the beginning of therapy. Amitriptyline improves insomnia associated with Migraine by reducing the sleep latency.[28]

CONCLUSION

Amitriptyline is low dosages is effective in controlling both headache as well as other symptoms associated with Migraine. Patients derive significant benefit from prophylaxis with Amitriptyline within three months of therapy. Though a lower dosage of 5 mg is effective in control of all symptoms, the better control of symptoms with Amitriptyline 10 mg without significantly raising the incidence of adverse effects makes it a better choice for prophylaxis.

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