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ARTICLE

Amitriptyline and aerobic exercise or amitriptyline alone in the treatment of chronic migraine: a randomized comparative study

Amitriptilina e exercício aeróbico ou amitriptilina isolada no tratamento da migrânea crônica: um estudo randomizado e comparativo

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ABSTRACT

To compare the preventive treatment benefits of amitriptyline and aerobic exercise or amitriptyline alone in patients with chronic migraine. **Method:** Sixty patients, both genders, aged between 18 and 50 years, with a diagnosis of chronic migraine, were randomized in groups called amitriptyline and aerobic exercise or amitriptyline alone. The following parameters were evaluated: headache frequency, intensity and duration of headache, days of the analgesic medication use, body mass index (BMI), *Beck Depression Inventory* (BDI) and *Beck Anxiety Inventory* (BAI) scores. **Results:** In the evaluated parameters, was observed decrease in headache frequency (p=0.001), moderate intensity (p=0.048), in headache duration (p=0.001), the body mass index (p=0.001), *Beck Depression Inventory* (p=0.001) *and Beck Anxiety Inventory* scores (p=0.001), when groups were compared in the end of third month. **Conclusion:** In this study, the amitriptyline was an effective treatment for chronic migraine, but its efficacy was increased when combined with aerobic exercise.

Keywords: chronic migraine, adults, prophylaxis, amitriptyline, aerobic exercise.

RESUMO

Comparar os benefícios do tratamento preventivo em pacientes com migrânea crônica utilizando a amitriptilina associada ao exercício aeróbico ou amitriptilina isolada. **Método:** Sessenta pacientes de ambos os sexos com idade entre 18 e 50 anos e com diagnóstico de migrânea crônica foram randomizados para receber amitriptilina e orientados a: praticar exercícios aeróbicos ou somente a amitriptilina isolada. Os seguintes parâmetros foram avaliados: frequência, intensidade e duração da cefaleia, dias de uso de medicação analgésica, índice de massa corporal (IMC), e pontuação nas escalas de *Beck Depression Inventory* (BDI) e *Beck Anxiety Inventory* (BAI). **Resultados:** Nos parâmetros avaliados, houve redução na frequência da cefaleia (p=0,001), intensidade moderada (p=0,048), na duração (p=0,001), no índice de massa corporal (p=0,001), e pontuação nas escalas *Beck Depression Inventory* (p=0,001) e *Beck Anxiety Inventory* (p=0,001), quando os grupos foram comparados ao final do terceiro mês. **Conclusão:** A amitriptilina foi um tratamento eficaz para a migrânea crônica, mas sua eficácia foi maior quando combinada com exercício aeróbio.

Palavras-chave: migrânea crônica, adultos, profilaxia, amitriptilina, exercício aeróbio.

Chronic migraine is a disabling disease, with a negative impact on the individual's ability to perform daily activities[1] affecting 2% to 3% of the general population[2] and with the prevalence in Brazilian population of 5%[3].

The quality of life in patients with chronic migraine have significant impairments compared to the healthy population and also when compared to other chronic conditions[4], and 85% of these patients have disabling attacks, justifying the introduction of prophylactic treatment[5].

In episodic migraines, amitriptyline has been used as prophylactic therapy in the last 45 years, and is generally accepted as an effective drug[6].

In addition to reducing the frequency, duration and intensity of headache attacks, therapy with amitriptyline may improve the response to acute treatment, reduce disability, and reduce associated economic costs[7,8].

The use of amitriptyline for treatment of migraine resulted in 50% reduction in the headache frequency.

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Studies demonstrated reduction in headache intensity and frequency of amitriptyline group compared to the group venlafaxine[9], reduction in the frequency and duration of headache compared to placebo[7]. Others studies observed similar results[10,11].

A significant reduction in the use of analgesic medication was related after prophylaxis with topiramate (50-100 mg/day) associated with amitriptyline (10-20 mg/day) in migraneurs with overuse of analgesic medicines[12] .

The use of amitriptyline for treatment of migraine requires initial doses of 10 to 25 mg, and the effective therapeutic dose ranges from 25 to 200 mg[13].

Studies with amitriptyline demonstrate limited evidence that the treatment may be beneficial for patients with chronic migraine[14].

Although several studies addressing prophylactic treatment for episodic migraine[6,7,8,9,10,11,12,13,14], only topiramate[15] and the botulinum toxin[16] were effective in placebo-controlled studies for the prophylactic treatment of patients with chronic migraine.

In addition to the prophylactic drug therapies, multiple studies have shown benefits of non-pharmacological interventions such as aerobic exercise[17,18,19,20,21,22,23,24]. Exercise of moderate intensity and practiced regularly can promotes muscle relaxation, improved cardiovascular fitness and also reduces the frequency, intensity and duration of headache attacks[19].

Hypotheses for the mechanisms by which exercise may reduce headache include decreased peripheral sensitization and activation of descending inhibitory pathways[25].

Studies where the exercise was supervised by a physical therapist demonstrated higher patient compliance[18,19,20]. However, even the studies without supervision, with exercises performed at home, positive results have been reported[20,21]. Despite of positive findings, these studies showed some limitations as a lack of control groups and subjective endpoints.

The aim of this study was to compare the combination of amitriptyline and aerobic exercise with amitriptyline alone in the prophylactic treatment of patients with chronic migraine, in a randomized controlled open label trial. The following parameters were evaluated: headache frequency, intensity and duration of headache, days of the analgesic medication use, body mass index (BMI), *Beck Depression Inventory* (BDI) and *Beck Anxiety Inventory* (BAI) scores.

METHOD

Over a 2-year period (June 2010 through June 2012), patients newly admitted to the out-patient Division of Investigation and Treatment of Headaches (DITH) of the *Universidade Federal de São Paulo* (Unifesp), both genders, aged between 18 and 50 years, all diagnosed with chronic migraine by the criteria of "The International Classification of Headache Disorders (ICHD-II, 2004)"[26], were included in the studies.

Inclusion criteria: patients diagnosed with chronic migraine, normal cardiac and neurological examination, who had not been practicing exercise for at least 3 months.

Exclusion criteria: previous use in the last year of medication with action in the central nervous system, including migraine prophylactics, other systemic, neurological and psychiatric disorders, inability to understand verbal commands and to perform aerobic exercise, not treatment compliance during the study.

In neurological evaluation, patients with medication overuse were instructed to perform a washout of all analgesic medicines and an abortive therapy with naproxen sodium 550 mg maximum twice a week and non-pharmacological practices were oriented. In psychological evaluation, patients were instructed to fill out *Beck Depression Inventory* and *Beck Anxiety Inventory*. After neurological and psychological evaluation patients were simple randomized, using computer-generated random numbers, in two groups:

- Amitriptyline alone: patients using amitriptyline (25 mg/day);
- Amitriptyline and aerobic exercise: patients using amitriptyline (25 mg/day) combined with aerobic exercise.

In the aerobic exercise program patients were instructed to perform a 40 minutes fast walk outdoors with a frequency of 3 times/week for 12 consecutive weeks[27] and daily, fill out a headache questionnaire. All patients received written instructions and performed a training session with physiotherapist.

Instruments used in the amitriptyline group and aerobic exercise: headache questionnaire, explanatory leaflet about the warm-up exercises, spreadsheet with hours of exercise performance, Borg scale[28] and measurement of heart rate on the initial and final walk.

Instruments used in the amitriptyline group alone: headache questionnaire.

The following parameters were evaluated: headache frequency (days/month), headache intensity 1 (mild), 2 (moderate) and 3 (disabling), duration/day of headache (6h, 12h, 18h e 24h), analgesic medication use (days/month), body mass index, *Beck Depression Inventory* and *Beck Anxiety Inventory* at baseline and in the end of the 3rd month. Also the patients were weekly assessed by telephone calls and informed the study authors about the evolution of proposed therapies.

The study was submitted and approved by the local Ethic Committee in Research, and all participants signed an informed consent form, but they were able to leave the study anytime and for any reason.

Table 1. Patients in amitriptyline alone (n=30) and amitriptyline and aerobic exercise group (n=30) according to the average age, gender and average onset migraine.

Variable	Group Amitr alone±SD	Group Amitr and exer±SD	p-value
Average age (y)±SD	35±8	31±9	0.170
Gender (%) – F:M	88:12	79:21	0.370
Average onset of migraine (y)±SD	17±10	13±11	0.189

Statistical analysis

For statistical analysis, Student's *t*-test was used. The significance level was $p \leq 0.05$. The Minitab was Statistical Software utilized.

RESULTS

Sixty patients were randomized for the study, 30 in amitriptyline alone group and 30 amitriptyline and aerobic exercise group.

In amitriptyline alone group 4 withdrew from the study for not using the medication correctly or not could tolerate the medication side effects (drowsiness and dry mouth) and in amitriptyline and aerobic exercise group 6 withdrew for non-adherence to proposed physical treatment.

The comparison of mean age, gender, and onset time of migraine between the groups were shown in Table 1.

Fifty patients reached the end of study. In the evaluated parameters, was observed decrease in headache frequency (p=0.001), duration of headache attacks (p=0.001) intensity moderate (p=0.048), the body mass index (p=0.006), *Beck Depression Inventory* (p=0.001) *and Beck Anxiety Inventory* scores (p=0.001) between the groups amitriptyline alone (n=26) and amitriptyline and aerobic exercise group (n=24), as summarized on Table 2.

DISCUSSION

This study showed that the combination of a prophylactic drug therapy amitriptyline with a non-pharmacological treatment aerobic exercise was effective as a preventive therapy as compared with amitriptyline alone.

There is no consensus in the literature about how patients with chronic migraine should be instructed to

Table 2. Results of headache frequency (days/month), duration and intensity of headache attacks (attacks/month), use of analgesic medication (days/month), body mass index (BMI), *Beck Depression Inventory* (*BDI*) and *Beck Anxiety Inventory* (*BAI*) scores at baseline and the end of the 3rd month in amitriptyline alone (n=26) and amitriptyline and aerobic exercise group (n=24).

Variable	Evaluation	Group Amitr alone±SD	Group Amitr and exer±SD	p-value
Frequency	initial	25±6.31	23±6.11	
	3rd month	13±6.41	5±2.21	0.001**
Duration (6h)	initial	1±3.14	4±9.74	
	3rd month	4±2.94	3±1.79	0.017*
Duration (12h)	initial	13±7.50	3±12.1	
	3rd month	1±4.62	6±1.74	0.001**
Duration (18h)	initial	5±9.13	2±3.26	
	3rd month	3±2.53	1±1.02	0.733
Duration (24h)	initial	20±13.9	20±11.0	
	3rd month	3±6.19	0	0.001**
Intensity 1 (mild)	initial	10±8.68	8±8.38	
	3rd month	5±3.18	3±2.16	0.528
Intensity 2 (moderate)	initial	13±6.89	14±7.57	
	3rd month	6±4.75	3±1.86	0.048*
Intensity 3 (disabling)	initial	6±5.50	6±6.55	
	3rd month	2±2.65	0	0.093
Analgesic Medication	initial	20±9.63	16±8.95	
	3rd month	3±2.99	1±1.48	0.752
BMI	initial	24±2.66	24±2.57	
	3rd month	25±2.92	23±2.64	0.006**
BDI	initial	14±11.45	10±6.70	
	3rd month	10±11.20	6±5.69	0.001**
BAI	initial	16±15.85	15±8.91	
	3rd month	10±12.10	8±7.17	0.001**

*p-value=0.05; **p-value=0.001.

perform aerobic exercise[19], so the parameters of intensity, frequency and duration of exercise were based on the parameters used for the healthy population[27].

The regular practice of aerobic exercise seems to benefit patients with migraine[17,18,19,20,21,22,23,24]. These benefits could be related to increased production of beta-endorphins[18] or changes in levels of nitric oxide during aerobic exercise[17]. Controlled studies are needed to define the optimal frequency and intensity of exercise[20].

Studies showed difference in pain intensity between groups[19,24] and this study also showed a significant reduction in these evaluated groups.

Despite of findings of decreased intensity, duration and frequency of headache in physically active people, there are few studies about the real influence of exercise in patients with headache[21].

Many patients with chronic migraine report that exercise exacerbates their headaches[20]. However, in this study was not observed worsening of headache in chronic migraine patients.

Obesity is a risk factor to migraine chronicity[29]. Despite the weight gain, the amitriptyline group alone had a reduced frequency of headache attacks. The combination of amitriptyline and aerobic exercise resulted in no increase in body mass index, therefore, in addition to resulting in greater efficacy of headache prevention, exercise can also prevent the adverse effect of weight gain associated with the use of amitriptyline.

This study had some limitations such as the small samples of patients evaluated, the aerobic exercise have been done by patients without supervision. However other studies without supervision and with the exercises performed at home led to similar results[18,19,20,21].

In conclusion, the therapy with amitriptyline was effective as a prophylactic treatment for patients with chronic migraine, however the combination of amitriptyline and aerobic exercise resulted in an even greater reduction in the frequency, duration and intensity of headache, in body mass index, *Beck Depression Inventory* and *Beck Anxiety Inventory scores*.

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