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ORIGINAL ARTICLE

Comparison of Treatment Efficacy in Migraine Patients treated with Nortriptyline and Caffeine Cessation vs Nortriptyline without Caffeine Cessation

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ABSTRACT

Background: The usage of caffeine as a psychostimulant is prevalent worldwide. However, consuming excessive amounts of caffeine can result in various acute and chronic biological and physiological alterations, which can lead to symptoms such as cognitive impairment, depression, fatigue, insomnia, cardiovascular changes, and headaches.
Aim: The objective of this study was to compare the treatment efficacy in migraine patients treated with nortriptyline and caffeine cessation versus nortriptyline without caffeine cessation.
Method: It's a randomized controlled trial. Research was conducted at Department of Neurology, Sir Ganga Ram Hospital Lahore. This study involved 76 patients of both genders, aged between 18-60 years diagnosed with migraine within the past 6 months which were randomly divided into two treatment groups. Patients in both the groups received nortriptyline. However, those in the experimental group were also advised to avoid caffeine intake.
Results: The outcome variable was the efficacy of treatment which was labeled if the patient had ≤1 episode of headache/week after 4 weeks of treatment. The mean age of the patients was 33.5±12.3 years. There were 27 (35.5%) male and 49 (64.5%) female patients. The frequency of treatment efficacy was significantly higher in patients treated with nortriptyline and caffeine cessation as compared to those treated with nortriptyline without caffeine cessation (78.9% vs. 39.5%; p-value<0.001).
In our current practice we don't prohibit caffeine use during treatment of patients with migraine which might be a cause for treatment failure and patient's dissatisfaction. If the results of the present study reveal that caffeine 14 cessation may improve treatment outcome of migraine patients, it will enable better management of such patients presenting in future clinical practice.
Conclusion: In the present study, caffeine cessation was found to be associated with a significantly higher frequency of treatment efficacy among patients receiving nortriptyline for migraine regardless of patient's age, gender, BMI, duration of disease, and number of headache episodes per week before the start of treatment which necessitates that caffeine cessation should be advised in such patients to improve the treatment response in future clinical practice.
Keywords: Migraine, Nortriptyline, Caffeine Cessation, Headache, Nortriptyline, neurological disorder

INTRODUCTION

Migraine is a complex disorder influenced by genetics, and is characterized by episodes of moderate to severe headache, which typically occur on one side of the head, and are often accompanied by nausea, increased sensitivity to light and sound, and can last for several hours to days[1]. Migraine is a leading cause of disability and can result in a loss of work productivity. The recurrent nature of migraine attacks and their duration make chronic migraine a significant economic burden on society[2]. Although some individuals may only experience mild symptoms, migraine is a widespread condition that is ranked by the World Health Organization as the third most common medical condition and the second most disabling neurological disorder globally. The general population has a 12% prevalence rate of migraine over a year[3].It's not clear exactly what causes migraine[4,5].

Recent progress in comprehending the pathophysiology of migraine has led to the development of both pharmacological and non-pharmacological therapies. These treatments target specific mechanisms that are known to contribute to the disorder, resulting in improved management of patients with migraine. Despite the availability of several treatments for migraine, they are not always fully effective, and patients remain dissatisfied with the recurrence of migraine attacks[6]. Infrequent caffeine intake can have analgesic effects or enhance the effectiveness of other pain relievers. However, chronic and repeated consumption of caffeine has been linked to an elevated risk of developing analgesic overuse headache, chronic daily headache, and physical dependence[7]. The existing evidence on the interaction of caffeine and headache in migraine patients is controversial where some studies advocate its use[8] or at least prohibit its cessation during treatment claiming cessation of caffeine may precipitate attacks of headache[9] while others claim vice versa and discourage the use of caffeinated drinks during migraine treatment[10]. Thus, to date there has been a great degree of confusion surrounding the link between caffeine intake and migraine, and in current practice, migraine patients are not advised about the cessation of caffeine intake during treatment.

In a recent study, it was reported that the frequency of treatment efficacy was significantly higher in migraine patients who stopped caffeine intake during treatment as compared to controls (72.2% vs. 40.3%: p=0.002)[11].

In light of this evidence, caffeine cessation may improve the treatment outcome of patients with migraine and should be advised in future medical practice. However, the existing evidence is limited to only a single above-mentioned study, there is no such local such published material that necessitates the present study. As already mentioned, in our current practice we don't prohibit caffeine use during the treatment of patients with migraine which might be a cause of treatment failure and patient dissatisfaction. If the results of the present study reveal that caffeine cessation may improve treatment outcomes of migraine patients, it will enable better management of such patients presenting in future clinical practice.

The objective of this study was to compare the treatment efficacy in migraine patients treated with nortriptyline and caffeine cessation versus nortriptyline without caffeine cessation.

MATERIALS AND METHODS

A randomized controlled trial was carried out at the Department of Neurology in Sir Ganga Ram Hospital Lahore over a period of six months. The study commenced after the synopsis was approved on September 16, 2021, and concluded on March 15, 2022. The sample size for the study was determined to be 76 cases, with 38 cases in each group. The calculation was based on an expected treatment efficacy rate of 72.2% with caffeine cessation and 40.3% without caffeine cessation in patients with migraine, with a power

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of 80% and a significance level of 5%[11]. The patients were chosen through a non-probability consecutive sampling method.

Inclusion Criteria

1. Patients of both genders with ages in the range of 18-60 years presenting with migraine
2. Patients diagnosed in the past 6 month's period only were included in the study.

Exclusion Criteria

1. Pregnant (as per dating scan) or lactating women.
2. Patients working at night shifts or those with disturbed sleep (<8 hours per 24 hours).
3. Patients using drugs that could interact with caffeine (e.g., tizanidine, lithium, phenylpropanolamine, clozapine, theophylline, adenosine, duloxetine, and ciprofloxacin) as per history and clinical record.
4. Patient's already taking nortriptyline for migraine for ≥1 week period.
5. Those who didn't give written informed consent to participate in the study.

Data collection procedure: Upon receiving approval from the hospital's Ethical Review Board, 76 patients (38 in each group) who met the inclusion criteria were selected from the Neurology Outpatient Department at Sir Ganga Ram Hospital in Lahore. These patients were provided with counseling and a comprehensive explanation of the study, after which they provided written informed consent and their detailed medical history was recorded. The patients were then randomly assigned to one of two groups using a lottery method.

Group A: Nortriptyline alone (n=38)

Group-B: Nortriptyline with caffeine cessation (n=38)

Patients in both the groups received treatment as per group. Patients were advised to take the medicines as prescribed and those who failed to comply were excluded from the study. Patients in the experimental group were advised to stop caffeine intake. Patients were evaluated 4 weeks after treatment and treatment efficacy was assessed as per operational definition. Confounding variables were controlled by exclusion. Patient's demographic details as well as efficacy of treatment were noted in the attached proforma.

Data analysis procedure: The data collected for the study was input and analyzed using SPSS version 17.0. Numerical variables such as age, duration of disease, BMI, and the number of headache episodes per week before starting treatment were presented as mean ± SD. Categorical variables such as gender and treatment efficacy were presented as frequency and percentage. The chi-square test was used to compare the frequency of treatment efficacy between the groups, with a significance level of $p \leq 0.05$.To address effect modifiers, the data was stratified by age, gender, duration of disease, BMI, and the number of headache episodes per week before starting treatment. The chi-square test was then applied post-stratification, with a significance level of $p \leq 0.05$.

RESULTS

The study included 76 patients with migraine aged between 18 to 60 years, with a mean age of 33.5±12.3 years. Majority of the patients 55(72.4%) were under 40 years of age, and 21(27.6%) patients were aged 40 years and above. There were 27(35.5%) male and 49(64.5%) female patients, resulting in a male to female ratio of 1:1.8. The mean BMI was 29.6±3.1Kg/m2, with a range of 22.3 to 34.3 Kg/m2, and 47(61.8%) patients were considered obese. The mean duration of disease was 3.68±1.63 months, ranging from 1 to 6 months, and the mean number of headache episodes per week was 4.24±1.18, ranging from 3 to 6.

Table 1 presents the comparison of various demographic and clinical characteristics between the two study groups, including mean age, mean BMI, mean duration of disease, mean episodes of headache per week before treatment, as well as the distribution of different subgroups based on age, gender, BMI, duration of disease, and episodes of headache per week before treatment. The results showed that both study groups were similar and comparable in all these aspects.

Patients who received treatment with nortriptyline and caffeine cessation demonstrated a significantly higher frequency of treatment efficacy compared to those who received treatment with nortriptyline alone, as indicated in Table 2. This significant difference was observed across various subgroups based on age, gender, BMI, duration of disease, and episodes of headache per week before the start of treatment when stratified, as presented in Table 3.

Table 1: Demographic Features of Study Groups (n=76)

Characteristic	Nortriptyline With Caffeine Cessation	Nortriptyline Without Caffeine Cessation	P-value
Age	33.4±12.2	33.6±12.5	0.941
<40 years	28 (73.7%)	27 (71.1%)	0.798
≥40 years	10 (26.3%)	11 (28.9%)	
Gender			
Male	13 (34.2%)	14 (36.8%)	0.811
Female	25 (65.8%)	24 (63.2%)	
BMI	29.5±3.3	29.7±2.9	0.781
Non-Obese	14 (36.8%)	15 (39.5%)	0.813
Obese	24 (63.2%)	23 (60.5%)	
Duration of Disease	3.66±1.65	3.71±1.63	0.889
≤3 months	20 (52.6%)	19 (50.0%)	0.818
>3 months	18 (47.4%)	19 (50.0%)	
Episodes of Headache	4.26±1.22	4.21±1.14	0.847
3-4	22 (57.9%)	21 (55.3%)	0.817
5-6	16 (42.1%)	17 (44.7%)	

Chi-square test and Independent sample t-test, Observed difference was statistically insignificant

Table 2: Comparison of Treatment Efficacy between the Study Groups (n=76)

Treatment Efficacy	Nortriptyline With Caffeine Cessation	Nortriptyline Without Caffeine Cessation	P-value
Yes	30 (78.9%)	15 (39.5%)	<0.001*
No	8 (21.1%)	23 (60.5%)	
Total	38 (100.0%)	38 (100.0%)	

*Chi-square test, * Observed difference was statistically significant*

Table 3: Comparison of Treatment Efficacy between the Study Groups across various Subgroups (n=76)

Subgroups	Efficacy of Treatment		P-value
	Nortriptyline With Caffeine Cessation	Nortriptyline Without Caffeine Cessation	
Age			
<40 years	22/28 (78.6%)	11/27 (40.7%)	0.004*
≥40 years	8/10 (80.0%)	4/11 (36.4%)	0.044*
Gender			
Male	11/13 (84.6%)	6/14 (42.9%)	0.025*
Female	19/25 (76.0%)	9/24 (37.5%)	0.006*
BMI			
Non-Obese	11/14 (78.6%)	6/15 (40.0%)	0.035*
Obese	19/24 (79.2%)	9/23 (39.1%)	0.005*
Duration of Disease			
≤3 months	16/20 (80.0%)	8/19 (42.1%)	0.015*
>3 months	14/18 (77.8%)	7/19 (36.8%)	0.012*
Episodes of Headache			
3-4	18/22 (81.8%)	9/21 (42.9%)	0.008*
5-6	12/16 (75.0%)	6/17 (35.3%)	0.022*

*Chi-square test, * Observed difference was statistically significant*

DISCUSSION

Migraine is a neurological condition that causes recurring headache episodes with accompanying symptoms such as sensitivity to light and sound, and autonomic symptoms[1]. The pathophysiological mechanisms of migraine are still not fully

understood, but it is believed that vascular dysfunction, cortical spreading depression, activation of the trigeminovascular pathway, and inflammation may be involved in pain generation[2]. Therefore, a multimodal treatment approach that takes into account these mechanisms may improve the quality of life for patients. In addition, dietary interventions have gained attention as a potential treatment option for migraine patients[11].

Since a significant portion of the population, including individuals who suffer from migraines, consume a substantial amount of caffeine daily, it is worth exploring whether caffeine has any impact on their headaches. While drinking coffee prior to a migraine attack may not be a genuine headache trigger, it may be the result of premonitory symptoms, such as fatigue, sleepiness, and yawning, which can signal the onset of a headache[8,9,10].

The mean age of the migraine patients in the present study was 33.5±12.3 years, which is consistent with the findings of a nationwide survey in Pakistan where a similar mean age of 34.4±11.0 years was reported[11,12]. Studies conducted at Pak Emirates Military Hospital Rawalpindi and Aga Khan University Hospital, Karachi reported a mean age of 33.4±3.8 years and 32±22 years, respectively, among patients with migraine[13,14]. Similarly, Jat et al. (2017) observed a mean age of 31.4±8.6 years among migraine patients at Jinnah Postgraduate Medical Centre, Karachi[15]. Comparable mean ages of 32.2±7.9 years, 38±12.7 years, and 30.8±9.5 years were also reported in studies involving Indian migraine patients.

In this study, it was found that patients with migraine had a higher prevalence of females with a male to female ratio of 1:1.8[13]. This finding is consistent with a study conducted at Pak Emirates Military Hospital Rawalpindi which reported a similar female predominance with a male to female ratio of 1:1.8. Additionally, studies conducted at Jinnah Postgraduate Medical Centre, Karachi and Aga Khan University Hospital, Karachi also reported a similar female predominance among patients with migraine, with male to female ratios of 1:1.9 and 1:1.9, respectively[14,15].

It was observed that 61.8% of patients with migraine were obese. A similar proportion of obese patients among Pakistani patients with migraine has been reported previously where it was observed that 60.0% of migraineurs were obese[14]. A comparable frequency of obesity among such patients in local population has also been reportedand observed to be 50.7% in a nationwide survey[1].

It was observed that treatment efficacy was significantly higher in patients treated with nortriptyline and caffeine cessation as compared to those treated with nortriptyline without caffeine cessation (78.9% vs. 39.5%; p-value<0.001). When stratified, similar significant difference was noted between the groups across various subgroups based on age, gender, BMI, duration of disease and episodes of headache per week before start of treatment.

Our observation is in line with a similar previously published study where it was reported that treatment efficacy was significantly higher in migraine patients who stopped caffeine intake during treatment as compared to controls (72.2% vs. 40.3%: p=0.002)[4].

The present study is first of its kind in local population and adds to the limited already published international research evidence on the topic. In the present study, we observed that migraine frequently involved younger females and majority of such patients were obese. We also found that caffeine cessation was associated with significantly higher frequency of treatment efficacy among patients receiving nortriptyline for migraine regardless of patient's age, gender, BMI, duration of disease and number of headache episodes per week before start of treatment. Thus, caffeine cessation should be advised in migraineurs to improve the treatment response in future clinical practice.

The present study had several strengths, including a large sample size of 76 patients and strict exclusion criteria. In addition, we used randomization and stratification to account for various effect modifiers. However, a major limitation of the study was the failure to consider other important aspects of patient management such as quality of sleep, job performance, and overall quality of life. Addressing these factors could have provided a more precise understanding of the role of caffeine cessation in the management of migraine patients. Therefore, future clinical research that includes these aspects is highly recommended.

CONCLUSION

In the present study, caffeine cessation was found to be associated with significantly higher frequency of treatment efficacy among patients receiving nortriptyline for migraine regardless of patient's age, gender, BMI, duration of disease and number of headache episodes per week before start of treatment which necessitates that caffeine cessation should be advised in such patients to improve the treatment response in future clinical practice.

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