



## Comparison of the Effect of Propranolol Combination with Cinnarizine and Propranolol in the Prevention of Acute Migraine Attacks

Dereen Adeeb Sheet<sup>1\*</sup>, Rashid Hamid Bibani<sup>2</sup>, Azad Hasan Kheder<sup>3</sup>

<sup>1</sup> Master Degree in Pharmacology, Department of Medical Education, College of Medicine, Hawler Medical University, Erbil, Kurdistan Region-Iraq

<sup>2</sup> PhD Clinical Neurology, Department of Medicine, College of Medicine, Hawler Medical University, Erbil, Kurdistan Region-Iraq

<sup>3</sup> FKBMS- Neurology, Department of Physiotherapy, Erbil Health Technical College, Erbil Polytechnic University, Erbil, Kurdistan Region-Iraq

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### ABSTRACT

Acute migraine attacks disrupt performance and reduce the quality of life. Therefore, efforts to prevent these attacks continue using different medications. This study aimed to compare the effect of cinnarizine combination with propranolol and propranolol with placebo in preventing acute migraine attacks. This study was a semi-experimental study performed on 120 adult patients with migraine referred to Department of Neurology in Rezgary Teaching Hospital in Erbil. Participants were randomly allocated to two groups control (propranolol) and intervention (propranolol with cinnarizine). The frequency, duration and severity of headache attacks were recorded and followed within two months. Data were analyzed with SPSS ver23 software and T-paired, independent T-tests and ANOVA. The average age of the participants was 34.54 years. 60% were female and 55% had a family history of migraine. The average frequency of headache attacks in the intervention group decreased by 75 % (from 15 times to 3 times) and a 50 % decrease in the control group (from 12 times to 6 times). The duration and severity of headaches in both intervention and control groups decreased ( $p < 0.001$ ), respectively. The average frequency, duration and severity of headache attacks in the first- and second months during treatment in the intervention group and control group were statistically different ( $p < 0.001$ ). The drug combination of propranolol with cinnarizine has an additional effect on reducing acute migraine attacks compared to propranolol alone.

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### Introduction

Migraine is a common and debilitating headache disorder that affects about 10% of men and 20% of women and is frequently identified by intense headaches on one side (1,2). Although this disease is the second leading cause of disability in life and is responsible for 3% of referrals to the emergency department per year, it is still less diagnosed and treated. Since the disability sources can be followed in childhood and youth for most adult migraine sufferers, the prevalence of migraine is more common between the ages of 18-44 years and it affects most people of working age (3,4). More than half of the people with migraine have described this disease as very damaging, which makes absolute rest during the headache inevitable (5).

Although regarding the clinical data there is a powerful hereditary component in migraine with aura, however signs and triggers is different very much between individuals and tracking the specific genetics of this situation (6). Migraine pathophysiology is complex and our understanding of it is progressing. Migraine has a genetic background that is accompanied by changes in ion channels and multiple neurotransmitter receptors. The cause of the headache is not yet clear, but it is likely to be related to the involvement of the hypothalamus and its connection with the Caudal Trigeminal Nucleus. Each person has a threshold for starting an attack, which can be influenced

by internal motives and environmental factors (7).

The International Classification of Headache Disorders is the standard for diagnosing migraine headache disorder. Migraine is a primary headache disorder, as opposed to a secondary headache which is caused by a secondary factor (8). Secondary headache has many possible reasons. Headache treatment depends on its cause (9). There are two main types of migraine, migraine with aura and migraine without aura. Migraine without aura requires at least five attacks for diagnosis. The headache is expected to occur between 4 and 72 hours. For diagnosis, at least two of the following characteristics are necessary: One-sided, throbbing, moderate to severe intensity and physical activity intolerance. Accompanying symptoms include sensitivity to the environment (photophobia and phonophobia) or digestive discomfort (vomiting or nausea). Pain is usually felt in the frontotemporal region. Migraine with aura is defined as symptoms of the central nervous system and at least two attacks are necessary for diagnosis. His symptoms are completely reversible. In general, migraine with aura includes visual, sensory or verbal symptoms (10).

Prevention is an important part of migraine treatment, but it can be easily overlooked when trying to find an effective treatment for the acute type. Approximately 40 percent of migraine patients need preventive treatment, but only 13 percent of patients use preventive drugs (11). Preventive treatment should be considered for any patient

\* Corresponding author. Email: [derin.adib@hmu.edu.krd](mailto:derin.adib@hmu.edu.krd)

who has at least three episodes of headache in one month. The goal of treatment is to reduce the intensity, duration and frequency of headaches. This treatment should prevent or reduce aura and other related symptoms. In addition to this, effective preventive treatment will reduce drug addiction and headaches (10). Successful treatment is the treatment that reduces migraine attacks by 50% within 3 months. Since migraine attacks are variable and treatment takes 2 to 6 months to reach maximum effectiveness, the recommended treatment period is usually 2 to 3 months (7,11,12).

For the prevention and treatment of migraine, many drugs such as beta blockers, antidepressants, ergotamine and other drugs have been proposed and used. And currently, researchers are trying to find drugs with a higher and better success rate (12). Amitriptyline is considered to treat different neuropathies, migraine prophylaxis, and fibromyalgia (13). In addition, antidepressants low doses are usually used to reduce chronic pain (14). Meanwhile, many studies have been conducted in the field of multi-drug combinations (12). In their study, Togha et al. (2012) pointed out that cinnarizine has a better effect than propranolol in the prophylaxis and treatment of migraine in children, and that it is safer (15). In other studies, the good effects of cinnarizine and propranolol on the prevention of acute migraine attacks in children and adults have been mentioned separately (16–18). But it has not been done in the field of combining these two drugs and comparing them with propranolol. Therefore, this study was conducted with the aim of comparing the effect of cinnarizine combination with propranolol and propranolol with a placebo in preventing acute migraine attacks.

## Materials and Methods

### Study design and setting

This study is a semi-experimental intervention study that has two control and intervention groups. This study was conducted on migraine patients who were referred to Department of Neurology in Rezgary Teaching Hospital in Erbil. in 2021.

### Participants

The sample size for this study considering alpha 0.05 and power 80% and effect size 0.5 and standard deviation 0.74, based on a similar study, for a higher power of the study 120 people (60 people in the intervention group and 60 people in the control) was considered. The study inclusion criteria include: adults over 18 years of age who were diagnosed with migraine after examination by a neurologist who is a member of the research team based on the migraine diagnosis criteria of the American Neurological Association, the number of monthly attacks was 2 to 8 attacks, the severity of the attacks has been so great that daily life activities have been affected. Patients with underlying systemic diseases, other types of headaches, neurological problems, pregnancy and drug sensitivity were not included in the study. Patients who refused to cooperate during the study and had drug sensitivity were excluded from the study.

### Instruments

A questionnaire was used to collect data, which includes two sections of demographic information such as age, gen-

der, Mean age of migraine onset (years), Family history of Headache, Family history of Migraine and Migraine type, characteristics of migraine Average duration of migraine headaches, Mean duration of attack (hour), Mean intensity of the attack (VAS), Mean number of days without attacks (day), Mean time between two consecutive attacks and Concomitant symptoms before Start treatment and the second part included frequency of attacks before the start of treatment, frequency of attacks in the first month of treatment, frequency of attacks in the second month of treatment and Scale of headache intensity It was surveyed.

### Intervention

Patients were randomly divided into two control and intervention groups based on the table of random numbers. The combination of propranolol and cinnarizine was prescribed for the intervention group, and the combination of propranolol and placebo was prescribed for the control group. After confirming the diagnosis of migraine by one of the researchers who is a neurologist, After obtaining informed consent to participate in the study, the eligible patients were introduced to another researcher and the necessary explanations about how to take the drugs and fill in the migraine registration form were provided to the patients. Patients recorded daily headache attacks in the relevant forms and the severity of headaches was also measured and recorded based on analog criteria. Patients were re-visited one month and two months after the start of treatment and the completed forms were collected by the research associate. In cases where the patient did not return on time, they were followed up by phone calls and data were collected.

### Data Analysis

SPSS version 23 software was used for data analysis. The frequency of data was used to describe nominal variables, and the mean and standard deviation of data were used for numerical variables. To examine the trend of headache attacks in each group after the intervention, at intervals of one month from the paired t-test, and to compare the trend of attacks in two months between two groups, independent t-test,  $\chi^2$  tests and One Way- ANOVA test with repeated measurements were used.

### Results

To conduct this study, patients referred to the Department of Neurology in Rezgary Teaching Hospital in Erbil. in 2021 who were eligible to enter the study were invited, and their number was 120. 60 people were in the intervention group (cinnarizine and propranolol) and 60 people were in the control group (propranolol and placebo). The 120 people participating in the study were those who regularly took medicine and were divided into two treatment groups.

Table 1 shows the demographic information and basic characteristics of migraine headaches in the participants of the study. Examining the gender variable of the participants in the study showed that in the cinnarizine and propranolol group, 17 were men and 43 were women. While in the propranolol and placebo treatment group, there were 39 women and 21 men, and there was no significant difference between the two treatment groups in terms of gender. The average age in the cinnarizine and propranolol

**Table 1.** Baseline demographic and characteristics migraine in the two treatment groups.

Baseline characteristics		propranolol combination with cinnarizine (n)	Propranolol (n)	P-value
Gender	male	17	21	0.5*
	Female	43	39	
Mean age (years)		34.54 (18-65) <sup>&amp;</sup>	31.58 (19-58) <sup>&amp;</sup>	0.04**
Mean age of migraine onset (years)		26.4 (20-54) <sup>&amp;</sup>	25.3 (19- 57) <sup>&amp;</sup>	0.03**
Family history headache	Yes	32	35	0.9*
	No	28	25	
Family history Migraine	Yes	36	30	0.2*
	No	24	30	
Migraine type	With Aura	9	14	0.05*
	Without Aura	51	46	
Average duration of migraine headaches		17.85 ± 15.45 <sup>&amp;</sup>	18.68 ± 16.14 <sup>&amp;</sup>	0.754**
Mean duration of attack (h)		14.2 (5-21) <sup>&amp;</sup>	15.4 (4-22) <sup>&amp;</sup>	0.001**
Mean intensity of the attack (VAS) <sup>#</sup>		8.5 (4-11) <sup>&amp;</sup>	9.1 (5-11) <sup>&amp;</sup>	0.001**
Mean number of days without attacks (h)		21.4 (18-26) <sup>&amp;</sup>	22.8 (19-27) <sup>&amp;</sup>	0.451**
Mean time between two consecutive attacks		4.2 (3-9) <sup>&amp;</sup>	5.7 (3-10) <sup>&amp;</sup>	0.01
Concomitant symptoms	Nausea	51	48	0.587*
	Vomiting	48	42	0.024*
	Photophobia	47	41	0.001*
	Phonophobia	51	46	0.684*

\*P-value based on  $\chi^2$  tests. \*\* P-value based on Student's t-test. & mean ± (SD), CI (confidence interval). # VAS visual analogue scale.

treatment group was 34.54 (18-65) and in the propranolol and placebo drug group it was 31.58 (19-58), and there is a significant difference in the average age of the two groups ( $P \leq 0.04$ ). Also, the results showed that the average age of the first migraine attack in the two treatment groups is significantly different ( $P \leq 0.03$ ) so this average for the cinnarizine and propranolol treatment group is 26.4 (20-54) and in the propranolol and placebo treatment group is 25.3 (57-19). Also, an examination of the family history of headaches and the family history of migraine in the two treatment groups did not show any significant difference. In the study of the type of migraine in the treatment group of cinnarizine and propranolol, 51 people were without aura, while in the treatment group of propranolol and placebo, there were 46 people without aura, which did not have a significant difference.

Examining the average headache duration per month showed that this average was  $15.45 \pm 17.85$  in the cinnarizine and propranolol treatment group and  $16.14 \pm 18.68$  in the propranolol and placebo treatment group, which did not have a statistically significant difference. Examining the duration of migraine attacks in terms of hours in two treatment groups, there is a statistically significant difference ( $P \leq 0.001$ ) that the average duration of attacks in the propranolol and placebo treatment groups with values of 15.4 (4-22), is more than the cinnarizine and propranolol treatment group with values of 14.2 (5-21). Examining the severity of headache attacks in terms of (VAS) showed that this value was 8.5 (4-11) for the cinnarizine and propranolol treatment group and 9.1 (5-11) for the propranolol treatment group that this variable has a significant difference in the two groups ( $P \leq 0.001$ ). Examining the number of days without migraine attacks in the two treatment groups did not show any significant difference. Examining the duration between two consecutive migraine attacks

in two groups showed a significant difference ( $P \leq 0.01$ ) and this average time between two migraine attacks was higher in the propranolol and placebo treatment groups. Examining simultaneous symptoms were investigated in two treatment groups. In the two treatment groups, no significant difference was seen in nausea and phonophobia, but two groups had significant differences in vomiting and photophobia (Table 1).

The effect of therapeutic interventions in two treatment groups on the frequency of migraine attacks was investigated. This study includes the number of attacks in two groups before therapeutic interventions, one month after therapeutic interventions and two months after therapeutic interventions.

The results showed that the number of attacks decreased significantly in both treatment groups. The average number of attacks in the cinnarizine and propranolol treatment group was 15 attacks before the start of treatment and 3 attacks in the second month of treatment, which significantly reduced the number of attacks ( $P \leq 0.01$ ). The average number of attacks in the propranolol and placebo treatment groups was 12 attacks before the start of treatment and 5 attacks in the second month of treatment, although the number of attacks has decreased significantly, the difference is not significant ( $P=0.146$ ) (Table 2).

Examination of the pain intensity scale was done in three categories: mild, moderate and severe.

In the mild pain scale, the mean attacks in the cinnarizine and propranolol treatment group increased in the first month, while it decreased in the second month of treatment. In the propranolol and placebo treatment group, the number of attacks increased in the first month but decreased in the second month of treatment. The average number of attacks in the second month of treatment showed a statistically significant difference ( $P \leq 0.003$ )

**Table 2.** Comparing the frequency of migraine headaches before treatment with the first and second month after starting treatment.

Group	frequency of attacks before the start of treatment (mean ± SD)	frequency of attacks in the first month of treatment (mean ± SD)	frequency of attacks in the second month of treatment (mean ± SD)	P-value*
propranolol combination with cinnarizine	15.65 (11.25)	7.42 (6.59)	3.41 (2.97)	0.001
Propranolol with placebo	12.35 (9.65)	8.14 (7.64)	5.57 (4.13)	0.146

\* P-value based on One-Way ANOVA.

**Table 3.** The frequency of migraine headache attacks Mean the number.

Scale of headache intensity	Treatment	Mean number of migraine attacks ± (SD)		
		Before treatment	First month	Second month
Mild	propranolol combination with cinnarizine	0.52 ± (0.89)	1.68 ± (1.85)	0.34 ± (0.52)
	Propranolol with placebo	0.64 ± (0.85)	0.94 ± (1.05)	1.24 ± (1.46)
	P-value*	0.68	0.041	0.003
Moderate	propranolol combination with cinnarizine	5.4 ± (2.6)	3.09 ± (2.65)	0.86 ± (1.3)
	Propranolol with placebo	5.68 ± (2.94)	4.45 ± (3.54)	3.34 ± (4.11)
	P-value*	0.84	0.24	0.035
Sever	propranolol combination with cinnarizine	3.5 ± (2.84)	4.54 ± (4.21)	1.4 ± (0.8)
	Propranolol with placebo	4.07 ± (3.87)	3.41 ± (2.13)	2.06 ± (1.66)
	P-value*	0.32	0.41	0.05

\* P-value based on One-Way ANOVA.

that the average number of attacks in the cinnarizine and propranolol treatment group was lower than the propranolol and placebo treatment group. In the average pain scale, the average attacks in the cinnarizine and propranolol treatment groups were reduced in the first and second months of treatment. In the treatment group of propranolol and placebo, the number of attacks was reduced in the first and second months. The average number of attacks in the second month of treatment showed a significant difference ( $P \leq 0.035$ ) that the average number of attacks in the cinnarizine and propranolol treatment group was significantly lower than the propranolol and placebo treatment group. In the severe pain scale, the mean attacks in the cinnarizine and propranolol treatment group increased in the first month, while they decreased in the second month of treatment. In the treatment group of propranolol and placebo, the number of attacks was reduced in the first and second months. The average number of attacks in the second month of treatment showed a significant difference ( $P \leq 0.05$ ) that the average number of attacks in the cinnarizine and propranolol treatment group was significantly lower than the propranolol and placebo treatment group (Table 3).

## Discussion

In this study, the two treatment methods of cinnarizine and propranolol were compared with propranolol and placebo in reducing migraine attacks. The results showed that both treatment methods reduce the number of migraine attacks, but Cinnarizine and propranolol treatment methods were more effective in reducing the number of attacks and pain intensity compared to propranolol and placebo treat-

ment methods and this difference has shown a significant difference in the two months after the treatment.

According to the World Health Organization (WHO), the prevalence of headache disorders in the world's adult population is estimated at 50%. About 75% of adults will have experienced a headache during 2021, and of these, 30% will have experienced a migraine headache. Considering that migraine is recurrent and accompanies a person for life, its headache is not only painful but also debilitating. In the Burden of Disease Study, Shamshin migraine is the cause of years lost due to disability (YLD). Also, the results have shown that people with migraine are more prone to anxiety and depression than other people (19).

Cinnarizine appears to be as effective and safe as other preventive medications for migraine, but the quality of the evidence for the effectiveness of cinnarizine among adults with migraine is relatively low. In the review study Togha et al. (2020) it has been shown that cinnarizine drug is effective in reducing migraine attacks and the severity of headaches, which is consistent with the results of the present study (20).

In the study of Bhat et al. (2017) with the aim of evaluating propranolol, flunarizine and divalproex sodium in the prevention of migraine, the results showed that the time of migraine attacks, the intensity of attacks and the intensity of headache in the three treatment groups showed significant differences and the results showed that all three drugs have the same effect in the treatment of the disease, while in the present study, despite the effect of both drugs in the treatment of the disease, the effects of cinnarizine and propranolol were shown to be more than propranolol and placebo (21).

Cinnarizine drug is prescribed as a first-line drug for the treatment of vertigo as a drug whose effects on nausea and vomiting and other diseases have been proven. Cinnarizine has the property of anti-vascular contraction and blood viscosity reduction. In a review study conducted by Kirtane et al. (2019) aimed at the effects of cinnarizine combined with other drugs in the treatment of various diseases, Its results have shown that the combination of this drug with other drugs will have a better effect in the treatment of various diseases (22), which is consistent with the current study that the combination of cinnarizine with propranolol is more effective than the effect of propranolol with placebo. In other studies that evaluated the effectiveness of cinnarizine in preventing attacks and pain intensity in migraine patients, the results are consistent with the results of the present study that this drug alone or together with other drugs had significant effects in controlling the disease (23–25).

Examining the demographic variables of the patients in the present study showed that the gender of the patients, the history of headaches and the history of migraine in the family have no significant difference. The study by Kati-beh et al. (2021) also found no difference in demographic variables, which results are in line with the results of the present study (26). Examining the age of the participants showed that there is a significant difference in the average age of the people and the average of the two groups is different, which is similar to the results of the study by Togha et al. (2012) that the average age of the participants in the study was different is consistent (15).

In examining the characteristics of migraine patients, the results showed that the average age at the onset of migraine attacks, the duration of migraine attacks, the intensity of attacks and the time interval between two attacks have significant differences while in the study of Alebrahim et al. (2019) these differences do not exist in the characteristics of migraine patients (16). Also, the presence of accompanying symptoms in patients such as nausea and phonophobia was also a significant difference, which has not been seen in other studies (27,28).

### Limitation

Considering that this study was conducted in a medical center, the results may be influenced by confounding variables and uncontrolled factors.

Therefore, it is recommended that these examinations be carried out in several treatment centers.

### Conclusion

The results showed that the two drugs cinnarizine and propranolol are effective and useful in reducing the number of attacks and the intensity of attacks and preventing migraine headaches among people who suffer from migraine. Although extensive studies have been conducted in the field of migraine prevention, the best drug has not yet been introduced with certainty, and more studies are needed to find the best drug or drug combination and make final statements. The present findings show that the effect of cinnarizine and propranolol together is more effective than propranolol alone for preventive treatment.

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### Interest conflict

The authors have no conflicts of interest to declare.

### Author's contributions

All authors passed the criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

### Data Availability

The authors guarantee that the data of this research will be provided at the request of other researchers.

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