

## Efficacy of Enalapril in Migraine Prophylaxis: A Randomized, Double-blind, Placebo-controlled Trial

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### ABSTRACT

**Background:** Some angiotensin converting enzyme (ACE) inhibitors have previously been shown to be effective in migraine prophylaxis. The aim of this study was to evaluate whether Enalapril is effective in migraine prophylaxis.

**Methods:** In this randomized, double-blind, placebo-controlled clinical trial, the effects of 10 mg Enalapril given daily were compared with those of matched placebo in 40 migraineurs for 2 months. Response to treatment was assessed at 0, 1, and 2 months after the start of intervention according to headache parameters like frequency, severity, and duration. This trial is registered with Iranian Registry of Clinical Trials (IRCT), number IRCT138711011570N1.

**Results:** A significant effect on reducing migraine attack more than 50% at first and second months ( $P=0.016$ ) occurred in Enalapril group. Indeed, at the first and second months of treatment, the severities ( $P=0.000$  and  $P=0.000$ ) and duration ( $P=0.037$  and  $0.003$ ) in the Enalapril treated group were significantly lower than in the placebo group.

**Conclusion:** Enalapril may be effective in migraine prophylaxis according to its effect in decreasing the frequency, severity, and duration of headaches. The results support the previous suggestions on usage of ACE inhibitors in migraine prophylaxis.

**Keywords:** Angiotensin converting enzyme inhibitors, Enalapril, migraine disorders

### INTRODUCTION

Migraine is the most common headache disorder occurring in humans.<sup>[1]</sup> Because of its high prevalence and also its possible relation with some severe disorders like stroke<sup>[2,3]</sup> among the general population, finding drugs which can be used for its prophylaxis seems to be important. Although the exact mechanism of its action is unknown, the rennin-angiotensin system (RAS) has an important role in migraine pathophysiology,<sup>[4]</sup> and both angiotensin converting enzyme inhibitors (ACEIs)<sup>[5,6]</sup> and angiotensin receptor blockers (ARBs)<sup>[7]</sup> exhibit efficacy for migraine prophylaxis.

The aim of this study was to evaluate the possible role of Enalapril

in improvement of headache characteristics of migraineurs.

## METHODS

### Study population

Patients who attended the neurology clinics of Al-Zahra hospital, Isfahan, between July 2008 and June 2009 were enrolled for the study. Patients who were diagnosed as migraineurs without aura in accordance with the International Headache Society criteria (second edition) (IHS 1.1)<sup>[8]</sup> and agreed to participate in the study after they were explained about the risks and benefits of Enalapril were enrolled in the study.

Patients who had hypertension, Diabetes Mellitus, coronary artery disease, known liver or kidney disorders, morbid obesity (body mass index  $>35$  kg/m<sup>2</sup>), current cigarette smoking, abuse of alcohol or other substances, sinusitis, tension-type headache more than 5 days per month, and less than four migraine attacks per month were not included in the study.

Exclusion criteria were hypersensitivity to ACEIs, pregnancy and lactation, and presenting with Enalapril complications which could not be tolerated. All of the patients had used at least one first-line prophylactic drug without any advantage in the past. None of the patients had previously used ACEIs or angiotensin-II receptor blockers.

### Study design

In this randomized clinical trial, during the baseline period of 1 month, no prophylactic medication was used by the patients. After this time, complete physical examination especially neurological examination was done in all patients. The headache impact test (HIT-6) questionnaire was used to evaluate the characteristics of patients' headaches (mean of severity, duration of headaches, and frequency in a month). Then, patients were randomized using a computer-generated randomization list to receive 5 mg Enalapril or placebo twice a day for 2 months. The placebo (made by Isfahan Pharmacy faculty, Isfahan University of Medical Sciences, Isfahan, Iran) was matched with 5 mg Enalapril tablets (Sobhan Darou, Tehran, Iran) in all characteristics. During the study, patients were educated to complete a record about the details of each headache attack (including severity, duration,

and frequency). Severity of each attack was evaluated by visual analog scale (VAS) from 1 to 10. Patients were allowed to control their acute migraine attacks with nonsteroidal anti-inflammatory drugs (NSAIDs). During these 2 months, patients were recommended not to use any drugs which have an effect on migraine characteristics. Every 2 weeks, all the patients were evaluated about Enalapril complications and details of their headaches by a person blinded to Enalapril and placebo treated groups. After these 2 months, all patients were recalled and complete examination was done again and completed diary was given back.

In this study, the hypothesis that using 10 mg Enalapril daily would make the patients' clinical status, especially their headache frequency, better was evaluated.

### Standard protocol approvals, registrations, and patient consents

The study was approved by the ethical committee of the Isfahan University of Medical Sciences. Written informed consent was obtained from all patients participating in the study. This trial is registered with Iranian Registry of Clinical Trials (IRCT), number IRCT138711011570N1.

### Statistical analysis

We calculated that a sample size of 43 patients was required to identify a difference of 1.5 in the number of migraine attacks between groups with 80% power, with  $P=0.05$  as the level of significance, and assuming a common SD of 2.5 for Enalapril and placebo treatment groups.

A 10% dropout rate was factored in, resulting in a planned sample size of 48 patients.

The results are expressed as mean  $\pm$  standard error (SE). Mean of severity of attacks, duration of each attack, and frequency (attacks/month) were calculated before, after 1 month, and after 2 months from start of the study. Differences between the groups were examined by independent-sample *t* test and within the groups were determined by repeated-measure analysis of variance (ANOVA), and if they were significant, the results were analyzed with paired-sample *t* test. *P* value of 0.05 was considered significant. Statistical analyses were performed with SPSS16 software by a person who was blinded about the details of research.

## RESULTS

### Demographic information

Forty migraineurs were enrolled in this study between July 2008 and June 2009. Six (15%) patients were males and 34 (85%) were females. Six patients were not enrolled in the study because they did not match the inclusion criteria and four patients refused to sign the informed consent paper. No one dropped out during the study period.

The mean of patients' ages was  $34.42 \pm 1.82$  years (with a range of 10–57 years). These patients were randomly divided into 21 and 19 subjects as the case and control groups, respectively. These people have suffered from migraine headaches about  $74.40 \pm 7.54$  months.<sup>[9]</sup>

The details of patients' demographic data are summarized in Table 1.

### Headache parameters

The patients' headache parameters including headache severity, headache duration, and headache attack frequencies are summarized in Table 2.

### Headache severity

As demonstrated in Table 2, the headache severity decreased significantly in the case group from baseline to both first ( $P=0.000$ ) and second ( $P=0.000$ ) months, but the differences in severity between the two months of treatment were not significant ( $P=0.2$ ). There was not any significant difference of headache severity in the control group throughout the study.

According to statistical analysis, the means of headache severities before beginning the intervention in the two groups were not different significantly ( $P=0.297$ ), but in the first ( $P=0.000$ ) and second ( $P=0.000$ ) months of treatment, the severity in the Enalapril treated group was significantly lower than in the other group.

### Headache duration

According to Table 2, in comparison with baseline, the mean of headache duration (hours per attack) in the first and second months of treatment decreased dramatically in the case group ( $P=0.009$  and  $0.004$ , respectively). However, there was no significant difference between the two months ( $P=0.267$ ). In the control group, the headache duration did not change significantly.

**Table 1:** Demographic information of patients

	All patients	Case group	Control group	Comparison of the two groups	P-value
Gender (male/female)	6/34	5/16	1/18		0.105
Age (years)	$34.42 \pm 1.82$	$37.19 \pm 2.17$	$31.36 \pm 2.89$		0.112
Family history	77.5%	81%	73.7%		0.816
First-degree family history	47.5%	47.6%	47.4%		0.107
Second-degree family history	2.5%	4.8%	0		
Third-degree family history	2.5%	4.8%	0		
Family history in two degrees	25%	23.8%	26.3%		
Migraine history (months)	$74.40 \pm 7.54$	$86.00 \pm 11.52$	$61.57 \pm 8.90$		

**Table 2:** Patients' headache parameters

	Before treatment	At the 1 <sup>st</sup> month	At the 2 <sup>nd</sup> month	F*	P-value*
Headache severity in case group (1–10)	$8.28 \pm 0.40$	$4.67 \pm 0.31$	$4.08 \pm 0.50$	28.692	0.000
Headache severity in control group (1–10)	$8.84 \pm 0.31$	$8.26 \pm 0.35$	$8.00 \pm 0.54$	1.661	0.204
Comparison between groups** (P-value)	0.297	0.000	0.000		
Headache duration in case group (hours)	$16.00 \pm 3.32$	$6.86 \pm 0.87$	$5.94 \pm 0.78$	9.157	0.001
Headache duration in control group (hours)	$12.23 \pm 1.53$	$10.71 \pm 1.59$	$10.96 \pm 1.41$	1.331	0.290
Comparison between groups** (P-value)	0.327	0.037	0.003		
Headache frequency in case group (attacks per month)	$13.16 \pm 2.00$	$10.42 \pm 1.83$	$9.95 \pm 1.97$	9.133	0.001
Headache frequency in control group (attacks per month)	$9.57 \pm 1.69$	$12.84 \pm 1.84$	$10.78 \pm 1.90$	3.373	0.058
Comparison between groups** (P-value)	0.185	0.360	0.762		

\*Repeated-measure ANOVA \*\*Independent samples *t*-test

**Table 3:** Summary of studies about headache prevention related substances influencing renin-angiotensin system

Study	Drug	Duration of study	Number of subjects	Adverse effect	Type of study	Year	Efficacy outcome	Type of headache population
Sicuteri <sup>[10]</sup>	Captopril	8 weeks	--	--	Open study	1981	Frequency of headache	Hypertensive patients with headache
Paterna <i>et al.</i> <sup>[12]</sup>	Captopril	4 months	26	---	A randomized double-blind study	1992	Related to changes in frequency, duration, or severity of headache attacks	Migraine headache
Bender <sup>[11]</sup>	Enalapril, Lisinopril	3 months to 3 years	17	Cough occurred in four patients	Open study	1995	Frequency of headache	Migraine headache
Eitman <i>et al.</i> <sup>[15]</sup>	Losartan (reference drug)	4-54 weeks	27 studies (12, 110)	--	Meta-analysis	2002	Headache frequency	Headache in hypertensive patients (circumstantial study)
Schrader <i>et al.</i> <sup>[5]</sup>	Lisinopril	12 weeks	30 participants and 30 placebo	Three withdrew from the study because of fatigue, dizziness, exanthema, and monarthritits	A randomized double-blind study	2001	Related to changes in frequency, duration, or severity of headache attacks	Migraine headache
Onder <i>et al.</i> <sup>[14]</sup>	ACE inhibitor (Enalapril, Captopril, Lisinopril, Ramipril)	12 weeks	762 patients	---	Open study	2003	Headache frequency	Hypertensive patients (circumstantial study)
Rahimtoola <i>et al.</i> <sup>[13]</sup>	ACE inhibitor or angiotensin receptor antagonist	24 months	47 patients with RAS drugs and 48 with diuretics	---	Open study	2004	Therapeutic intensity	Migraine headache
Tronvik <i>et al.</i> <sup>[7]</sup>	Candesartan	12 weeks	30 patients with Candesartan and 30 placebo	Nonsignificant adverse effect in comparison with placebo	A randomized double-blind study	2003	Related to changes in frequency, duration, or severity of headache attacks, level of disability, doses of triptans, doses of analgesics, acceptability of treatment, days of sick leave, and quality-of-life variables	Migraine headache
Schuh-Hofer <i>et al.</i> <sup>[16]</sup>	Lisinopril	4 weeks	21 patients	Three patients dropped out because of cough	Open study	2007	Related to changes in frequency, duration, or severity of headache attacks	Migraine headache
Camarda <i>et al.</i> <sup>[18]</sup>	Enalapril	12 months	1 patient	---	Case report	2003	Headache frequency	Migraine headache

On comparison of the two groups, the durations were significantly different at both months of treatment ( $P=0.037$  for the first month and  $P=0.003$  for the second month), in spite of the baseline duration times ( $P=0.327$ ).

#### Headache attacks frequency

As summarized in Table 2, the mean of headache attack frequencies in the Enalapril group was significantly lower at the first ( $P=0.001$ ) and second ( $P=0.005$ ) months of treatment in comparison to the baseline values, but the mean of the first month was not different from that of the other month ( $P=0.497$ ). In the control group, compared to baseline values, the frequency significantly increased at the first month ( $P=0.027$ ) but there was not much difference at the second month ( $P=0.443$ ).

On the other hand, 47.61% (10 persons) of Enalapril treated group and 10.52% (2 persons) of the control group experienced at least 50% improvement in headache severity from baseline to 2 months and this difference between groups was significant ( $P=0.016$ ). Also, the Odds Ratio for this 50% change was 7.72 (with a range of 1.41–42.17).

## DISCUSSION

In this double-blind, placebo-controlled, randomized clinical trial, we observed that Enalapril decreased monthly headache frequency, severity, and duration.

Migraine prevention by substances influencing the RAS such as ACEIs or ARBs was first shown by an open study on Captopril in 1981.<sup>[10]</sup> Then, Bender<sup>[11]</sup> in a small open study and Paterna *et al.*<sup>[12]</sup> in a small randomized double-blind study showed that Enalapril, Lisinopril, and Captopril can prevent migraine attacks, and also some circumstantial studies in hypertensive patients indicated the preventive effect of RAS-related drugs.<sup>[13-15]</sup> One of these studies was a meta-analysis<sup>[15]</sup> which showed the Odds Ratio for having headache per unit dose of the reference drug Losartan (as an ARB) equal to 0.81 (95% CI: 0.68–0.93). Two other randomized, controlled, and blinded studies were performed by Schrader *et al.*<sup>[5]</sup> and Tronvik *et al.*<sup>[7]</sup> on Lisinopril as an ACEI and Candesartan as an ARB, respectively. Recently, an open label study<sup>[16]</sup> on low-dose Lisinopril indicated the efficacy of this drug close to that of beta-blockers with good tolerability. Also, a study reported a 68-year-old

woman with a 20-year history of migraine with aura, who experienced a control of her attacks after using Enalapril 10 mg/day for treatment of hypertension.<sup>[17]</sup>

This study, as far as we know, is the first controlled and blinded trial which showed the effect of Enalapril on the control of migraine headache. In this study, we showed that the side effect of this drug is only cough and this drug is reasonably tolerable. Only three patients experienced a short period of self-limited cough and it did not force them to discontinue the study. The other patients did not have any other side effects. Table 3 shows all studies about headache prevention related substances influencing RAS.

There are some conceivable explanations for the beneficial effects of ACEIs on migraine. ACEIs modify sympathetic tone and promote degradation of proinflammatory factors such as substance P, enkephalin, and bradykinin.<sup>[5,18]</sup> Furthermore, they can modulate the endogenous opioid system receptors.<sup>[19]</sup>

Some authors believe that intrinsic RAS of the brain within the blood-brain barrier, working independent of the peripheral RAS, has effects on neurons, astrocytes, and endothelial cells, and influences cerebral vascular tone, NO production, and Calcitonin gene-related peptide Calcitonin gene-related peptide (CGRP) levels.<sup>[4]</sup>

Also, as we have shown in a previous study that this prophylactic effect might be because of endothelial function improvement which occurred in these patients by using ACEIs like Enalapril.<sup>[9]</sup>

## CONCLUSION

This study has shown that Enalapril can be a good preventive choice for migraine attacks and can decrease the headache parameters like frequency, severity and duration. Two limitations of this study were the small sample size and also the design of the study which could be a cross-over study.

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