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Inhibitory control of angiotensin-converting enzyme by ramipril in migraine

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Abstract

Background: Renin-angiotensin systems (RAS) are involved in the physiology of migraine. Ramipril is an angiotensin-converting enzyme inhibitor. We tested whether ramipril has an effect on migraine. *Methods:* The study was designed as a prospective open-labeled trial in a single center. All patients were asked to maintain a headache diary. Ramipril was administered at 5mg/day (2.5mg twice a day) and subjects were checked every 4 weeks up to 12 weeks. *Results:* The mean number of headache days was 19.9 ± 11.2 days per month at baseline, and 12.0 ± 11.5 at 12 weeks (p<0.001 vs. baseline) with a responder rate of 41.9%. Stratified analysis by migraine frequency (15 days a month ≥ vs. <15 days a month) did not show a difference. Mean blood pressure was not altered.
Conclusions: Ramipril prevented migraine attacks independently from blood pressure. This result supports a link between renin-angiotensin system and migraine pathophysiology (Clinicaltrials.gov identifier: NCT01402479).

INTRODUCTION

The Renin-angiotensin system (RAS) is a hormone system that regulates long-term blood pressure and extracellular volume in the body. Angiotensin converting enzyme inhibitors (ACEIs) have been used as anti-hypertensives and for cardiovascular protection.[1]

Evidences of migraine physiology by substances influencing RAS have been accumulating since an open study using captopril in 1981.[2] Lisinopril, an ACEI, and candesartan, an angiotensin II receptor blocker have been shown to be effective migraine prophylactic agents.[3,4]

Ramipril is an ACEI that decreases cardiovascular events with involvement in RAS.[1] It is lipid-soluble, and thus can cross blood brain barrier. However, it is unknown whether the effect of ramipril on RAS can also affect migraine physiology in subjects with hypertension. In this study, we attempted to test the hypothesis on human subjects of the involvement of RAS in migraine, by confirming the efficacy of ramipril in migraineurs with hypertension.

METHODS

This research was approved by the Institutional Review Board of Seoul National University Hospital (Reference no. #0408-131-005). Written approval from the Institutional Review Board was received and all subjects provided informed consent before study participation.

Experimental subjects were recruited in the headache clinic at Seoul National University. They were diagnosed as migraine without aura or chronic migraine, meeting the criteria of the International Classification of Headache Disorders-2nd edition (ICHD-II). All patients had hypertension. Medication overuse headaches were excluded in this study. Migraineurs should be aged 20 to 70 years old with the ability to read and understand the self-report scales, including the headache diary, used in this study.

Exclusion criteria were the following conditions: 1) Treatment with other ACEI or medication that may affect ARS; 2) Treatment with migraine prophylactic medications or anti-hypertensive agents including βadrenergic receptor or calcium channel blockers; 3) Past history of hepatic or renal dysfunction, an abnormal electrocardiography, a psychiatric disorder, a history of substance abuse, pregnancy or lactation, use of anti-psychotics, antidepressants, or anti-anxiety drugs.

All subjects were asked to maintain a diary, in which details on the number of migraine attacks and adverse events were recorded. Baseline migraine days were obtained from diaries for the baseline phase. Ramipril was initially administered at 5mg/day (2.5mg twice

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a day) and subjects were assessed every 4 weeks up to 12 weeks. All patients were allowed to use secondary anti-hypertensive medications if the blood pressure rose further. In this case, the patients were excluded from the study. The outcome measure was determined by the number of days with migraine (migraine days) per month. The responder rate was defined as the percentage of subjects showing a 50% or greater reduction in attack frequency at 12 weeks compared to the baseline headache days. Efficacy analyses were performed on an intention-to-treat (ITT) basis. The last observations of patients who dropped-out were carried forward to subsequent assessment periods (LOCF). The paired Student's *t*-test and the Chi-square test was used for responder rate comparisons between migraineurs. SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses, and a two-tailed probability value below 0.05 was considered to indicate significance.

RESULTS

Forty three experimental subjects with migraine and hypertension participated in the study (men: women=16:27, mean age=59.9±9.6 years), and 39 completed the three months protocol. Among the four subjects (9.3%) that withdrew from the study, 3 reported no effect (one at 4 weeks, two at 8 weeks), and one reported a full improvement (at 8 weeks) as the reasons of withdrawals. Thus, the overall responder rate was 25% in the withdrawn patients. Among the 43 participants, 3 subjects reported side effects, including one mild cough and 2 anorexia. These adverse events were mild and transient. We observed no treatment-emergent conditions or study withdrawal related with the adverse events. Ramipril with a dose of 5mg/day in this study did not significantly lower the blood pressure.

The mean values of migraine days were 19.9 ± 11.2 days per month at baseline, 17.0 ± 11.6 at 4 weeks (p=0.013 vs. baseline), 14.5 ± 11.9 at 8 weeks (p<0.001 vs. baseline), and 12.0 ± 11.5 at 12 weeks(p<0.001 vs. baseline) (LOCF, Figure 1). The overall responder rate was 41.9% at 12 weeks. After stratification according to baseline migraine days (days ≥15/month vs. <15/month) and excluding medication-overuse headache, 28 subjects were subcategorized into 'chronic migraine' excluding medication-overuse headache. However, the responder rates were not different between this group and the group with less than migraine frequency of <15/month (46.4% and 33.3%, respectively, p=0.407 by chi-square test).

We compared the ramipril group in the current study to a historic control group in a randomized controlled trial in migraine prophylaxis in our institution [9]. The control group was treated with placebo drug twice daily. The placebo group showed 1.48% reduction in headache frequency at 4 weeks after the treatment. In the current study, the ramipril group showed 14.58% reduction in the frequency at 4 weeks. In addition, the placebo group showed 10.3% reduction at 6 weeks and the ramipril group showed 27.1% reduction in the frequency during the similar period (at 8 weeks). Also, in the responder rate analysis, the rate was 27.9% in the historic placebo group and 41.9% in the current study with ramipril treatment. Accordingly, based in this comparison to the historic control, the ramipril treatment appeared

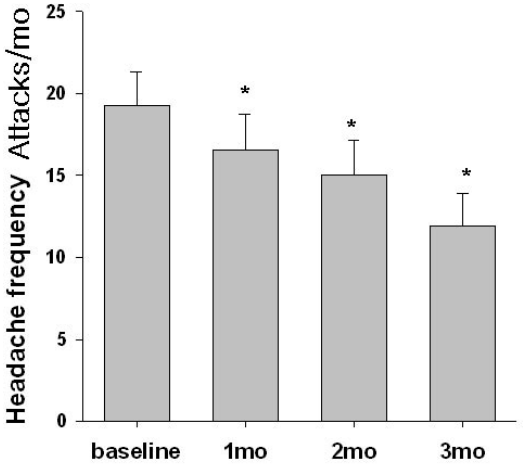

Figure 1. Mean headache days. Ramipril 5mg/day was started at week 0 and mean headache days decreased by 40% after the 12 weeks of ramipril administration. *p<0.05, **p<0.01 vs. baseline (week 0).

superior to the placebo control treatment to prevent migraine.

DISCUSSION

The purpose of present study was to determine whether ramipril, an angiotensin-converting enzyme inhibitor, could alter the migraine frequency by affecting renin-angiotensin system. The results decreased migraine attacks, implying that the renin-angiotensin system influences the physiology of migraine pathogenesis.

The first-line prophylactic medications for migraine include propranolol, tricyclic anti-depressant, valproate, and topiramate. These drugs modulation of serotonin, blockage of voltage-dependent sodium channels, augmentation of $GABA_A$ receptors, antagonism of the AMPA/kainate receptor, or inhibition of the carbonic anhydrase enzyme, which may account for the underlying mechanisms of migraine (Angehagen *et al*.[8]). In this experiment, alteration of migraine frequency by angiotensin metabolism, ramipril, suggest that RAS is involved in the pathogenesis of migraine.

In addition, high plasma ACE activities in migraineurs suggests the involvement of RAS in the pathophysiology of migraine.[5] Because ramipril reduced migraine attacks without reducing blood pressure, our study suggests that migraine physiology may be a dissociable phenomenon from blood pressure regulation.

Intrinsic RAS exists in the brain within the blood-brain barrier working independently of peripheral RAS. It affects endothelial cells, thus influencing cerebral vascular tone, nitric oxide production and CGRP (Calcitonin gene related peptide) levels, a transmitter which may also mediate migraine physiology.[6,7] Therefore, it can be postulated that ramipril may enhance the threshold for the initiation of migraine attack by inhibition of ACE activities of the brain. Since several other studies have observed that the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers prevent migraines[10], RAS is likely to be involved in the development of migraine attacks.

There are several limitations in this study. The mean age of the study subjects was older than that of general population, since they were co-morbid with hypertension. This may limit generalizability. Although we administered ramipril twice daily, once daily dosing of ramipril might have improved the drug compliance. Because this study was an open-label non-randomized study conducted in a single center, further randomized controlled studies in non-hypertensive subjects are warranted.

In conclusion, our study found that ramipril, an ACEI, is potentially effective in migraine prophylaxis, suggesting involvement of RAS as a part of migraine physiology.

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DISCLOSURE

Conflict of interest: None

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