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Original Research Article

Lisinopril as a prophylactic agent for migraine: a randomised double blind placebo controlled cross over prospective study in Kashmir

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ABSTRACT

Background: Migraine is one of the commonest neurological disorder seen by neurologists. Many different medications are available to be used as prophylactic agent. We conducted this study to determine the efficacy of Lisinopril as a prophylactic drug for migraine in our region.
Methods: Our study is a randomised double blind, placebo controlled, cross over, prospective study. 60 patients were included in this study. Treatment period of 12 weeks with one 10 mg lisinopril tablet once daily for one week then two 10 mg lisinopril tablets once daily for 11 weeks, followed by a two week wash out period. Second treatment period of one placebo tablet once daily for one week and then two placebo tablets for 11 weeks. Thirty participants followed this schedule, and 30 received placebo followed by lisinopril. Primary end points were number of hours with headache, number of days with headache, number of days with migraine.
Results: Statistical analysis of data from 41 patients that completed this study revealed that hours with headache, days with headache, days with migraine, and headache severity index were significantly reduced by 16%, 16% , 23% and 17% , respectively, with lisinopril as compared to placebo.
Conclusions: This study favours lisinopril as an effective prophylactic drug for migraine. The adverse effects of lisinopril, though of significant frequency, have been mild to moderate in severity but were well tolerated by even normotensive subjects.

Keywords: Lisinopril, Migraine, Kashmir

INTRODUCTION

Migraine is said to be one of the most prevalent health disorders worldwide, and the most frequent cause of headache consultation in the Americas, Europe, South-East Asia, and the Western Pacific.[1] In Asia the sex-specific migraine prevalence has been reported as 11.3% to 14.4% in women and 3.6% to 6.7% in men.[2]

The human angiotensin converting enzyme (ACE) gene consists of either an insertion (I) allele or a deletion (D) allele forming three possible genotypes: II, ID or DD.[3,4] Many studies have shown association of ACE gene I/D polymorphism with various medical conditions including migraine.[5-9] In addition the response to treatment has also shown an association with this polymorphism.[10]

On the basis of these studies, ACE inhibitor lisinopril was tried as a prophylactic agent for migraine showing good results.[11-14] No such study has been reported form our region, prompting us to conduct this study in which we attempted to see the efficacy of lisinopril as a prophylactic agent in migraine.

METHODS

It was a Randomised double-blind placebo controlled cross over prospective study done at Sheri-Kashmir Institute of Medical Sciences, Srinagar, over a period of eighteen months from July 2015 to December 2016. 60 patients of both sexes aged between 19 and 59 years who had migraine with or without aura, having two or more episodes per month for more than one year were included in this study. Data collected was analysed using SPSS software. We used the Wilcoxon test for paired samples for statistical analysis. Results were regarded statistically significant at the $p<0.05$ level. Proper approval was taken from Institutional ethical clearance committee. Informed consent was taken from all participating patients.

Patients who were excluded from this study were those who were pregnant/ lactating, had deranged renal function, hypersensitivity to lisinopril, hypertensive, history of angioedema or psychiatric disorders.

Sixty patients fulfilling the inclusion criteria were allocated to treatment by randomized procedure with 15 consecutive balanced blocks of four patients (two active, two placebo) each. A treatment period of 12 weeks with maximum 20 mg lisinopril, doubling every 2 days to reach a dose of 10 mg one daily in first weeks then two 10mg tables once daily for 11 weeks followed by a two weeks WASH OUT period with 1 tablet of placebo once daily. Then second treatment period of one fourth placebo tablet once daily double every two days to reach a dose of one tablet once daily in one week then two tablets a day for 11 weeks was given. 30 patients followed this schedule and 30 received placebo followed by lisinopril.

The main Out-Come measures included primary end points of number of hours with headache, number of days with headache, and number of days with migraine. The Secondary end point. Were headache severity index (headache in hours x severity (grade 1-4)), use of drugs for symptomatic relief, number of days as sick leave/inability to do activities of daily living and acceptability of treatment.

RESULTS

A total of 60 patients were included in this study. Ten out of 60 patients dropped out during the treatment period. Fifty patients maintained the headache diary for the full study period, out of whom, 9 were found to be non-complaint as per the left over tablet count at the end of the study.

Fourty one patients who completed the study with full drug compliance were evaluated for efficacy parameters during lisinopril versus placebo periods. A comparison of efficacy measures during 4 weeks run in period versus 12 weeks lisinopril treatment period (average adjusted for 4 weeks) was also made. The two treatment groups were also compared with respect to non-compliance, adverse effects drop out and changes in pulse and blood pressures and a statistical inference of differences was drawn thereof.

Patients comprised of 21 (35%) males with mean (SD) age of 28 (8) years and 39 (65%) females with mean (SD) age of 29(8) years. The difference in sex distribution is statically significant ($p=0.20$), while as the mean age (SD) in the two groups bears no statistical significance.

A total 37 (61.7%) patients had common migraine with mean age (SD) of 26.3 (6.95) years, comprising 25 (41.7%) females and 12 (20%) males. 23 (38.3%) patients had classic migraine with mean age (SD) of 32.04 (9.22) years. Of these 14 (23.3%) patients were females and 9 (15%) patients were males. None of these observations bears a statistical significance.

Table 1: Efficacy parameters lisinopril versus placebo group (12 weeks treatment) (n=41).

Efficacy parameters	Lisinopril group mean (SD)	Placebo group mean (SD)	Mean difference	P	Mean% reduction
Primary					
Hours with headache	124.76 (37.55)	152.51 (40.89)	27.76	0.000	15.96
Days with headache	17.98 (4.96)	21.54 (4.71)	3.56	0.000	16.06
Days with migraine	3.73 (3.75)	17.88 (4.05)	4.15	0.000	22.85
Secondary					
Headache severity index	302.9 (99.53)	375.07 (111.31)	72.17	0.000	17.22
Dose of abortive drugs	54.68 (16.86)	72.54 (21.10)	17.85	0.000	25
No. of Sick leaves	5.15 (2.76)	6.63 (3.40)	1.49	0.001	23

A total 26 (43.4%) patients experienced adverse effects during lisinopril treatment period. 13 (21.7%) patients developed cough, 12 (20%) patients developed symptoms of hypotension. 1 (1.7%) patient developed urticaria. In the placebo group, 7 (11.7%) patients developed adverse effects. 1 (1.7%) patient had cough, 6 (10%) had symptoms of hypotension. By McNemars matched pairs test, adverse effects are significantly more during lisinopril treatment period ($p<0.05$). 10 (16.7%) patients dropped out of the study, all during lisinopril treatment period, 5 due to severe cough, 4 due to symptoms of hypotension and 1 due to urticaria.

Table 2: Intention to treat analysis of efficacy parameters lisinopril versus placebo treatment group (n=50).

Efficacy parameters	Lisinopril group mean (SD)	Placebo group mean (SD)	Mean difference	P	Mean% reduction
Primary					
Hours with headache	126.82 (34.76)	154.72 (37.75)	27.9	0.000	16.05
Days with headache	18.34 (0.67)	21.68 (0.62)	3.34	0.000	14.94
Days with migraine	13.9 (0.49)	17.76 (0.53)	3.86	0.000	21.18
Secondary					
Headache severity index	306.60 (12.98)	379.84 (14.35)	73.24	0.000	17.52
Dose of abortive drugs	57.18 (2.35)	73.74 (2.78)	16.56	0.000	22
No. of Sick leaves	5.10 (0.38)	6.72 (0.45)	1.62	0.000	24

Table 3: Efficacy parameters during 4 weeks placebo run in period versus 12 weeks lisinopril treatment period (average adjusted for 4 weeks) (n=41).

Efficacy parameters	Lisinopril group mean (SD)	Placebo group mean (SD)	Mean difference	P	Mean% reduction
Hours with headache	49.10 (15.20)	41.58 (12.51)	1.82	0.000	13.55
Days with headache	7.83 (4.26)	5.99 (1.65)	1.84	0.004	16.46
Days with migraine	6.39 (4.15)	4.57 (1.24)	1.82	0.003	19.90
Headache severity index	126.54 (37.20)	100.96 (33.17)	2.5.58	0.000	19.85

There was a significant reduction in mean (SD) BP both systolic and diastolic (p=0.000) and mean pulse rate (p=0.006) in the lisinopril group.

For primary efficacy measures, the mean difference is 27.76 for hours with headache, 3.56 for days with headache and 4.15 for days with significant migraine headache, which are all statistically significant (p=0.000) as shown in Table 1. For secondary efficacy measures the mean difference is 7.217 for headache severity index (p=0.000). 17.85 for dose of abortive drugs (p=0.001) and 1.49 for number of sick leaves (p=0.001) which are all statistically significant. There is a significant mean percentage reduction of 16% for hours with headache, 16% days with headache, 23% for day with migraine and 17% for headache severity index in the lisinopril treatment group. The mean difference is 27.9 for hours with headache, 3.34 for days with headache, 3.86 for days with migraine, 73.24 for headache severity index, 16.56 for dose or abortive drugs and 1.62 for number of days with sick leave which is significant for all these efficacy parameters (p=0.000)as shown in Table 2. There is a significant mean reduction of 16% for hours with headache, 21% for days with migraine, and 18% for headache severity index, in lisinopril treatment group. There is also a significant 18%, 22% and 24% reduction is headache severity index, dose of abortive drugs and number of sick leaves respectively in the lisinopril treatment group.

As shown in Table 3, there is a significant mean difference of 7.25 for hours with headache (p=0.000), 1.84 for days with headache (p=0.004), 1.82 for days with migraine (p=0.003) and 25.58 for headache severity index (p=0.000). All being significantly decreased during lisinopril treatment period with a mean percentage reduction of 14% for hours with headache, 16% for days with headache, 20% for days with migraine and 20% for headache severity index.

DISCUSSION

Many drugs have been approved for the prophylactic treatment of migraine but adverse effects limit the long term use of these agents. Further the response to these drugs vary in different patients. Due to these reasons, the search for new agents to reduce the number and severity of migraine attacks is always going on. Lisinopril, a ACE Inhibitor has also been tried in migraine. With respect to efficacy parameters of lisinopril we followed the guidelines recommended by the International headache society committee on clinical trials in migraine, and in accordance with the declaration of Helsinki, using less ambiguous end points of number of days with migraine, number of days with headache and number of hours with headache.[15]

First study using lisinopril as a prophylactic agent for migraine was published in 2007 by Schrader et al.[11] That was a randomised, placebo controlled, crossover study in which 60 patients were included at the start but only 47 had complete data at the end of the study. In these 47 participants, hours with headache, days with headache, days with migraine, and headache severity index were significantly reduced by 20%, 17%, 21% and 20% respectively, with lisinopril compared with placebo. Days with migraine were reduced by at least 50% in 14 participants for active treatment versus placebo and 17

patients for active treatment versus run-in period. Intention to treat analysis of data from 55 patients supported the differences in favour of lisinopril for the primary end points. The mean percentage reduction for secondary efficacy parameters of headache severity index, dose of abortive drugs, and number of days with sick leaves was 20%, 22% and 10% respectively.

In 2007 Schuh-Hofer et al published their study were they studied low dose lisinopril (5 mg) for migraine prophylaxis.[12] It was an open label study in 21 migraineurs. Compared with baseline conditions, the attack frequency of migraine attacks was significantly reduced ($p<0.0005$). The number of acute migraine drugs dropped significantly ($p=0.002$). Three patients dropped out because of intolerable cough. This study suggests that even low dose lisinopril may be effective as an prophylactic agent, though its use may be limited by adverse effects like cough.

In our study efficacy parameters were assessed by paired sample statistics method which will have a power of about 93% to detect a group mean differentiation of 0.5 (SD), in a study including 60 subjects. A two tailed $p<0.05$ has been considered significant. Analysis of primary efficacy measure in 41 patients who completed the study with full compliance showed that there was a statistically significant ($p=0.000$) mean decrease of 27.76 for hours with headache, 3.56 for days with headache and 4.15 for days with migraine during lisinopril treatment period. For secondary efficacy parameters there was decrease of 72.17 for headache severity index ($p=0.000$) 17.85 for dose of abortive drugs ($p=0.001$) and 1.49 for number of sick leaves ($p=0.001$) in favour of lisinopril. All these differences are statistically significant.

These statistics translate into a significant mean percentage reduction 16% for hours with headache, 16% for days with headache, 23% for days with migraine 17% for headache severity index, 25% for dose of abortive drugs and 23% for number of sick leaves, favouring lisinopril against placebo. In the intention to treat analysis of efficacy parameters of 50 patients for 12 weeks treatment period (patients who provided complete record of whole study irrespective of drug compliance), there was a mean reduction of 27.9 (16%) for hours with headache, 3.34 (15%) for days with headache, 3.86 (21%) for days with migraine, 73.24 (18%) for headache severity index, 16.56 (22%) for dose of abortive drugs and 1.62 (24%) for number of days with sick leaves in favour of lisinopril, thus retaining the statistical significance ($p=0.000$) for all parameters.

The comparison of efficacy parameters during 4 weeks placebo run in period, versus 12 weeks lisinopril treatment period (average adjusted for 4 weeks) for 41 patients showed a significant mean difference of 7.25 for hours with headache ($p=0.000$), 1.84 for days with headache ($p=0.004$), 1.82 for days with migraine ($p=0.003$) and 25.58 for headache severity index ($p=0.000$), all being significantly decreased during lisinopril treatment period with a mean percentage reduction of 14%, 16%, 20% and 20% for hours with headache, days with headache, days with migraine and headache severity index respectively.

CONCLUSION

Our study reveals migraine to be a common ailment, more so in females, with common migraine dominating. Males and urban residents, present for treatment earlier as compared to their counterparts. This study favours linsinopril as an effective prophylactic drug for migraine with an overall reduction of about 18% for primary efficacy parameters of hours with headache, days with headache and days with migraine; and 20% reduction for secondary efficacy parameters of headache severity index, dose of abortive drugs and days with sick leaves. The adverse effects of lisinopril though of significant frequency have been mild to moderate in severity but were well tolerated by even normotensive subjects. However, lisinopril needs to be assessed for prophylaxis of migraine, in studies involving large number of subjects as there are no large population studies till date. In addition it needs to be studied in direct comparison with other drugs of proven efficacy in migraine, to assess its comparative efficacy.

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