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ROLE OF LISINOPRIL AS A PROPHYLACTIC AGENT IN MIGRAINE; A CROSS SECTIONAL PLACEBO CONTROLLED TRAIL.

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KEYWORDS : .

Introduction:
Migraine, a benign and recurring syndrome of headache, nausea, vomiting and/or other symptoms of neurological dysfunction in various admixtures, is the most common cause of headache, afflicting approximately 15% of women and 6% of men [1]. The International Headache Society has defined migraine as multiple attacks, each lasting 4 to 72 hours, of moderate to severe, unilateral pulsating headache aggravated by routine activities, and associated with nausea and/or vomiting, photophobia and phonophobia [2]. Migraine can begin at any age, most commonly the initial attack occurs during teenage, and by 40 years of age 90% of the sufferers have had their first attack. Although migraine can begin in older patients but it should be viewed with suspicion because a serious intracranial disorder like ICH, tumours (primary and secondary) temporal arteritis and glaucoma, could be masquerading as migraine. After puberty migraine is more common in females, whereas in children there is small male preponderance. Once migraine has developed it tends to recur with varying frequency throughout the patient's life, with a tendency to get milder and less frequent in later years of age[3].

Headache classification Committee of International Headache Society has classified migraine as:
1. Migraine without aura (common migraine).
2. Migraine with aura (classic migraine).
- Migraine with typical aura.
- Migraine with prolonged aura
- Familial hemiplegic migraine
- Basilar migraine
- Migraine aura without headache (migraine equivalents)
- Migraine with acute onset aura

3. Ophthalmologic migraine.
4. Retinal migraine.
5. Childhood periodic syndromes that maybe precursors or associated with migraine.
- Benign paroxysmal vertigo of childhood.
- Alternating hemiplegia of childhood.

6. Unclassifiable migraine like disorders [4,5].

Although migraine attacks have been classified into those with aura, they are not mutually exclusive and many patients have separate attacks of two types [3].

Migraine without aura is by far the most frequent type of vascular headache. There are no premonitory sensory, motor or visual symptoms. Migraine is likely to be a complex disorder with polygenic inheritance and a strong environmental component. Three main theories of pathogenesis are proposed; vascular theories, neuronal theory of migraine and the trigeminal nucleus caudalis activation theory. The role of 5-HT, dopamine and sympathetic nervous system has been studied extensively and drugs developed accordingly.

Unified theory of Migraine:
To better understand the various aspects of migraine pathophysiology, the concept of a "unified theory of migraine" has been put forward which states that migraine is a complex disorder with pre headache vasoconstrictor phenomenon representing a neurogenic vasospasm of the innervated vascular system with the consequent local metabolic abnormalities leading to prodromal symptoms. The parenchymal arteries responsive to focal metabolic demand as well as cranial arteries on the outside of head subsequently dilate, producing the familiar throbbing headache of migraine. The change in tone of extra cranial arteries provoke the release of multiple local chemical and vasoactive substances producing edema, sterile inflammation, lowering of pain threshold and clinical headache. The various neurotransmitters and vasoactive substances involved in the migrainous process are: Catecholamines, histamine, serotonin, tyramine, substance P, the slow reacting substance of anaphylaxis (SRSA), prostaglandins, peptide kinins, encephalins, β endorphins and tryptophan [6].

Recently Appenzeller has proposed that endothelial cells are highly active metabolic endocrine organs and produce different important substances including prostacyclin. Endothelium derived relaxing factor identical to nitric oxide (ERRF-NO) and endothelin I may be involved in the pathogenesis of migraine. Endothelium has ten times more vasoconstrictor action than angiotensin II and acts as a neurotransmitter resembling serotonin [7].

The ambiguity regarding the pathophysiology of migraine has resulted in a large number of drugs being used in the treatment and prevention of migraine. An improved knowledge of the mechanism of an attack would help clarify the pharmacological properties required by any new drug developed to be specifically prevented [8].

Migraine prophylaxis:
Indications
1. More than two attacks a month.
2. Regular single attack of disabling intensity lasting more than 24 hours.
3. Contraindication to symptomatic (abortive) therapy.
4. Substance abuse tendencies.
5. Regular absence from work or school, and substantial disruption of household and social responsibilities.
6. Intolerance or failed abortive therapy.

Drug Prophylaxis of Migraine:
A large number of groups of drugs have been tried and used in the migraine prophylaxis e.g. Beta blockers (propranolol, Nadolol,

Timolol, Atenolol), Calcium channel blockers (Verapamil, Nifidipine, Flunarizine). NSAIDS (Naproxen, Fenoprofen, Aspirin). Antidepressants (Amitiyptyline, Fluhexetiene). MAOIS (phenelzine). Anticonvulsants (valproic acid). Miscellaneous (Methysergide, Cyproheptadine, Lithium)[7].

All these drugs have proved limited efficacy with a large list of side effects, contra-indications and drug interactions, so their usefulness, as prophylactic drugs for migraine, when the drug is to be taken over a prolonged period of time, remains limited, leaving the field open for search of newer safe and effective drugs, which can be used over a prolonged period of time, co-prescribed with other drugs, as in co-morbid conditions.

Our present study is a step in the same direction, that is to evaluate the efficacy of a comparatively effective and safe drug lisinopril in the prophylaxis of migraine.

Lisinopril:
Lisinopril is a potent, long acting oral Angiotensin converting enzyme inhibitor active without metabolism. Peak plasma concentrations are achieved in 6 to 8 hours after a single dose. Plasma ACE activity falls progressively from 60 minutes after an oral dose of 10 mg to reach its minimum value at 6 hours, and suppresses ACE activity to less than 20% of basal activity for 24 hours.

Lisinopril is indicated in, hypertension, heart failure, acute MI and renal complication of diabetes. Contraindications, which are all relative, are bilateral renal artery stenosis, low B.P, high dose diuretic therapy, salt deplete states, renal impairment, pregnancy, lactation, potassium sparing diuretics, angioedema and hypersensitivity to lisinopril [9].

Lisinopril is well tolerated and the adverse events observed are cough and the symptoms associated with initial hypotension (dizziness and tendency to fate) especially in volume or salt depleted individuals. ACE inhibitors reset auto regulation of cerebral blood flow and marked pressure fall may be tolerated without symptoms. Hypotension may be minimized by liberal fluid and salt intake and reducing lisinopril to its lowest effective dose. In contrast with β blockers lisinopril can be used in patients with Asthma, intermittent claudication and cardiac conduction defects and is not associated with sexual dysfunction. Withdrawal of lisinopril is not associated with untoward effects. Tolerance is not a problem.

Proposed mechanism of action of lisinopril in migraine prophylaxis:
Lisinopril has various pharmacological effects that may be relevant in migraine, in addition to blocking conversion of Angiotensin I into Angiotensin II, it also alters sympathetic activity, increases prostacycline synthesis, inhibits free radical activity and blocks the degradation of bradykinin, encephalin and substance P [10,11]

Of great relevance is the recent finding that migraine without aura seems to be more common in people with ACE DD gene, and migraineurs with this gene have higher ACE activity and a higher frequency of attacks than other migraine sufferers [3].

Aims & Objectives
To determine the efficacy of ACE inhibitor Lisinoril" in the prophylaxis of Migraine and to determine the tolerability of Lisinopril.

Materials and Methods
Design: Randomized double blind placebo controlled cross over prospective study.

Participants: 60 patients of both sexes aged 19 to 59 years of migraine with or without aura, having two or more episodes per month for more than one year.

EXCLUSION CRITERIA:
1. Pregnancy and lactation.
2. Deranged renal function.
3. Hypersensitivity to lisinopril.
4. Hypersensitive patients.
5. H/O Angioedema.
6. Psychiatric disorders.

INTERVENTIONS:
1. Participants who satisfied the inclusion criteria had to
i. Give a written informed consent &
ii. Maintain a daily headache diary.
2. Participants entered a four weeks Placebo RUN IN to verify the frequency of attacks. Participants were instructed to take one tablet daily and continued in the study only if they got two or more migraine attacks during this period.
3. The participants maintained a daily headache diary and recorded the following:-
i. Presence of headache.
ii. Whether migraine or not.
iii. Duration of headache in hours.
iv. Severity of headache.
v. Accompanying:
* Nausea * Photophobia * Phonophobia
vi. Use of symptomatic drugs (total dose).
vii. Sick leave.
viii. Adverse effects if nay.
4. To obtain the requisite number of 60 patients to be randomized for treatment, 78 patients were inducted into the placebo run in period from outpatient clinic. 28 patients were excluded before being randomized for non-fulfilling inclusion criteria and other reasons.
5. Sixty patients fulfilling the inclusion criteria were allocated to treatment by randomization (two active, two placebo) each. A treatment period of 12 weeks with 2.5mg lisinopril doubling every 2 days to reach a dose of 10mg once daily in first week ***WASH OUT*** period of 1 tablet of placebo once daily. Then second treatment period of one fourth placebo tablet once daily doubled 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.
6. All tablets needed for the study were supplied to the participants in identical form and pack under three codes:
i. 16100 tablets of lisinopril (Hipril) 10mg packed in 100 vials of 161 tablets each bearing a label marked code B and S.No. 1 to 100 for drug treatment period of 12 weeks for 100 patients.
ii. 16100 tablets of placebo placed in 100 vials of 161 tablets each bearing a label marked code A and S.No. 1 to 100 for placebo treatment of 12 weeks for 100 patients.
iii. 4200 tablets of placebo packed in 100 vials of 42 tablets each bearing a label marked code P and S.No. 1 to 100 for a run in period of four weeks and washout period of two weeks for 100 patients.

These tablets were provided, packed, labeled and coded by a renowned pharmaceutical company of India, Micro Labs Ltd., No. 2, Queens Road, Bangalore, 560001, at concessional rates. The code was kept secret, and displayed at the end of the study, thus ensuring the double blind design of the study.

7. The patients were monitored as under at intervals shown against them:

Wk 1:	H.R.:	Syst. Exam:	B. Urea:
	B.P.:	N/L Exam:	S. Creatinine:
Wk. 5:	H.R.:	Syst. Exam:	
	B.P.:	N/L Exam:	
Wk. 7:	H.R.:	B. Urea:	
	B.P.:	S. Creatinine:	
Wk 17:	H.R.:		
	B.P.:		
Wk. 21:	H.R.:	B. Urea:	
	B.P.:	S. Creatinine:	
Wk. 31:	H.R.:	Syst. Exam:	

Each participant was asked to report back in case of any untoward effect.
8. We were provided with a sealed code for each individual patient that was to be opened in case of any emergency that required knowledge of treatment being taken.
9. After each treatment period patient was also asked about the acceptability of the treatment.
10. Participants were defined as compliant with treatment if they adhered to the drug regimen (>80% of tablets taken as determined by a tablet count at the end of treatment period) and had given complete data in the diary.
11. Participants who were all normotensive were advised to assume a

liberal fluid and salt intake during the study period.

MAIN OUTCOME MEASURES:

1. Primary end points.
1. Number of hours with headache.
2. Number of days with headache.
3. Number of days with migraine.

2. Secondary end points.
1. Headache severity index [(Headache in hours x severity grade 1-4)]
2. Use of drugs for symptomatic relief.
3. Number of days as sick leave/inability to do ADL(Here onwards referred to as number of days with Sick leave)

Observations

Out of 78 patients who were inducted into the placebo run in period from out patients clinic, 18 were excluded before being randomised for treatment, as six did not fulfil the inclusion criteria(less than two attacks per month), five patients belong to far-flung areas with no available contact, declined to follow-up and three patients having no apparent reason refused to continue in the study. Ten out of remaining 60 patients dropped out during the treatment period, 50 patients maintained the headache dairy 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 study. Forty-one patients who completed the study with full drug compliance were evaluated for efficiency parameters during Lisinopril vs. Placebo period. A comparison of efficacy measures during 4 weeks RUN IN period vs. 12 weeks of Lisinopril treatment period (average adjusted 4 weeks) was also made. The two treatment groups were also compared with respect to noncompliance, adverse effects, dropouts, change in pulse and BP and a statistical inference was drawn thereof

Out of total 60 patients, 35% were males and 65% females with the mean age of 29.38 $\pm$ 8 *years* in both the sexes; females outnumbering males. Thirty seven (61.7%) patients had common migraine, comprising of 41.7% females and 20% males. Twenty three (38.3%) patients had classical migraine, comprising of 23.3% females and 9% males, however none of these observations was statistically significant. Twenty six (43.4%) patients developed adverse effects during lisinopril treatment period. Thirteen (21.7%) developed cough, 20% developed hypotension and 1.7% developed Urticaria. In placebo group, 11.7% patients developed adverse events, 1.7% developed cough and 10% had symptoms of hypotension. Occurrence of adverse effects was statistically significant with the p value of <0.05 in lisinopril group, as a result 16.7% dropped out of lisinopril group, 5 due to cough, 4 due to hypotension and one due to Urticaria.

Ten percent of the patients became noncompliant during lisinopril treatment and 5% became so in placebo group. There was a significant reduction in mean $\pm$ *SD BP* in both systolic and diastolic BP (p=0.000) and a mean pulse rate (p=0.006) in the lisinopril group.

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

Efficacy Parameters	Lisinopril Group; Mean(SD)	Placebo Group; Mean(SD	Mean difference	P	Mean % Reduction
Primary					
1. Hours with Headache	124.76 (37.55)	152.51 (40.89)	27.27	.000	15.96
2. Days with Headache	17.98 (4.96)	21.54 (4.71)	3.54	.000	16.06
3. Days with migraine	373 (3.75)	17.88 (4.05)	4.15	.000	22.85
Secondary					
a. Headache severity index	302.9 (99.53)	375.07 (111.31)	72.17	.000	17.22
b. Dose of abortive drugs	54.68 (16.86)	72.54 (21.10)	17.85	.000	25
c. No. of sick leaves	5.15 (2.76)	6.69 (3.40)	1.49	.001	23

For primary efficacy measures [Table 1], the mean difference is 27.76 for hours with headache, 3.56 for days with headache and 4.15 for days with migraine. All these observations are statistically significant (p=0.000). For secondary efficacy measurers, the mean difference is 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 which are all statistically significant. There is a significant mean percentage reduction of 16% for hours with headache, 16% days with headache, 23% days with migraine and 17% for headache severity index in Lisinopril treatment group.

Table 2:Intention to treat analysis of efficacy parameters lisinopril versus Plecebo group (12 weeks treatment) n=50

Efficacy Parameters	Lisinopril Group; Mean(SD)	Plecebo Group; Mean(SD	Mean difference	P	Mean % Reduction
Primary					
a. Hours with Headache	126.82 (34.76)	154.72 (37.75)	279	.000	16.05
b. Days with Headache	18.34 (0.67)	21.68 (0,62)	3.34	.000	14.96
c. Days with migraine	13.9 (0.49)	7.76 (0.53)	3.86	.000	21.18
Secondary					
a. Headache severity index	306.60 (12.96)	379.84 (14.35)	73.24	.000	17.52
b.Dose of abortive drugs	57.18 (2.35)	73.74 (2.78)	16.56	.000	22
c.No. of sick leaves	5.10 (0.38)	72 (0.45)	1.62	.001	24

The efficacy parameters showed the mean difference is 27.8 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 of abortive drugs and 1.62 for number of days with sick leave which is significant for all thee parameters (P=.000) [Table 2]

There is a significant mean reduction of 16% for hours with headache, 21% for days with headache and 18% for headache severity index in Lisinopril treatment group. There is also a significant 18%, 22% and 24% reduction in headache severity index, dose of abortive drugs and number of sick leaves respectively in the lisinopril treatment group.

Table 3: Efficacy Parameters During 4 Week Placebo Run In Period Vs 12 Week Lisinopril Treatment Period (Average Adjusted For 4 Weeks) N=41

Efficacy Parameters	Lisinopril Group; Mean(SD)	Plecebo Group; Mean(SD	Mean difference	P	Mean % Reduction
Primary					
a. Hours with Headache	49.10 (15.20)	41.58 (12.51)	1.82 (7.25)	.000	13.55
b.Days with Headache	7.83 (4.26)	5.99 (1,65)	1.84	.004	16.46
c.Days with migraine	6.39 (4.15)	4.57 (1.24)	1.82	.003	19.90
d.Headache severity index	126.54 (37.20)	100.96 (33.17)	25.58	.000	19.85

There is a significant mean difference of 7.25 for hours with headache(P=.000), 1.84 for days with headache (P= .004),1.82 for days with migraine (P=.003) and 25.58for headache severity index (P=.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 [Table 3].

Discussion:

Our study is a randomized, double blind, placebo controlled, cross over study for prophylaxis of migraine involving 60 patients of both sexes with common or classic migraine (with lisinopril Vs placebo); patients had a minimum age of 19 years to give a legally valid consent and maximum age of 59 years, as by that age the prevalence and severity of migraine dies out and the catastrophic causes of headache, resembling migraine are more prevalent and thus would have needed extensive and costly imaging to exclude them [3,4]. The participants had to have a migraine duration of at least one year, which by and large excludes the sinister causes of headache needing investigation and urgent specific treatment.

In our study migraine is found to be significantly more common (65%

vs 35%) in females as compared to males (p=0.020). This observation is consistent with existing literature which states that 15% of women vs 6% of men are afflicted by migraine and that migraine is more common in females after puberty [1,3].

Common migraine has been more common as compared to classical migraine 61.7% vs. 38.3% (though not statistically significant for either sex) which is in accordance with world literature [2].

There is also evidence that common as well as classical migraine is more common in females as compare to males 41.7% and 22.3% vs. 20% and 9% respectively, though these differences are not statistically significant. Common migraine presents earlier mean age (SD) 26 (7) years vs 32 (10) years for classical migraine.

While studying the relation of migraine with rural vs urban residence, 40 (67%) of patients were rural residents and 20 (33%) were urban residents. The difference being statistically significant ($p<0.05$), which reflects the fact that the majority of our population is rural. In both rural and urban groups, common migraine dominated vs classical migraine (43% and 18% vs 23% and 15% respectively). These differences are not statistically significant. Urban patients having age of presentation 1 year earlier to that for rural patients which could be because of less literacy rate (and thus less awareness) and less excess to health care facilities in rural areas.

Regarding adverse effects in our 60 patients cough was observed in 13 (21.7%) patients, which as recorded in literature has been in the range of 0.4 - 20% in different studies [12-14]. Thus our study has recorded highest percent incidence, which may be attributed to otherwise high incidence of cough (other than lisinopril induced) associated illnesses in our population due to cold weather.

Giddiness, dizziness and fatigue (symptoms of hypotension) were observed in 12(20%) of patients. World literature mentions this adverse effect to be very common, and has been quantified in one of the studies to be about 27% [14]. The reason for a lower incidence in our patients, could probably because of increased fluid and salt intake by our patients which they were advised to assume.

Urticaria was observed in 1 (1.7%) patient as against the reported incidence of 0.1 to 0.2% [7]. No other adverse effects were observed in patients.

The incidence of adverse effects were 21.7%, 20% and 1.7% in the lisinopril group versus 1.7%, 10% and 0% in the placebo group for cough, symptoms of hypotension and urticaria respectively. These results when analyzed by McNemars matched pairs test for comparison of pooled effects, were found to be significant ($p<0.5$) being more during lisinopril treatment period.

Ten patients (16.7%) dropped out of the study, 5 because of severe cough, 4 because of symptoms of hypotension and 1 because of severe urticaria, while none of the patients dropped during placebo treatment period.

Six more patients (10%) became non-complaint while on lisinopril versus three patients (5%) during placebo treatment period as per the left over tablet count at the end of the study. This difference which is not statistically significant (p=.404) can be attributed to lisinopril related adverse effects, as other reasons provided by patients were common to both groups.

Dropout rate in our study has been 16% vs 8% in a previous study [14] which can be attributed to high incidence of severe cough in our patients.

The pattern of pulse and BP variation in lisinopril vs placebo groups revealed mean (SD) BP of 112/71 (5/4.5) and mean (SD) pulse rate of 76 (6) in lisinopril group versus 125/81 (7/5) and 80 (4) in placebo group. Thus though there is a significant reduction in both systolic and diastolic BP (p=0.000) and mean pulse rate (p=0.006) in the lisinopril group, but the mean fall has been only 13mm and 9mm for systolic and diastolic blood pressures respectively. These observations fall well within the vicinity of the results available in literature, wherein the difference though significant has been less than 10mm for both systolic and diastolic blood pressures. In one of the studies the drop in diastolic BP has been only 3mm and that in mean arterial pressure has been less than 20mmHg at a dose of 20 mg of enalapril wherein the drug was tried in normotensive patients[14,15].

With respect to efficacy parameters of lisinopril we followed the guidelines recommended by the International 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. Number of attacks were not used as an efficacy end point, because it needed to record a more difficult thing as to when the headache started and stopped, causing higher dropout rates. Further use of abortive drugs, modifies the attack pattern and it becomes difficult to assess the actual attack rate as per the definition of International Headache Society. Furthermore no data is available wherein attack frequency has been reliably assessed according to International Headache Society guidelines.

Crossover design of this single center study was chosen because lesser number of patients is needed as against a parallel group design. The disadvantages of a crossover study like period effect, crossover effect and high dropouts (only 8%) has been observed in similar studies, despite long duration of study. In our study dropout rate was 16%.

Results of this study in terms of efficacy parameters can be compared with the only study [14], conducted on similar pattern with efficacy parameters. Other prophylactic drug studies for migraine have been conducted in different designs and with different end points of efficacy, so cannot be compared directly with this study.

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. { table 1 }

For secondary efficacy parameters there was a 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 favor 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, favoring lisinopril against placebo.

These results match with the results of a previous study by Herald Schreder et al. for efficacy parameters except for the parameter of 'Days with sick leaves', where there has been a reverse trend.

The study had shown a mean percentage reduction of 20%, 17% and 21% in primary efficacy parameters of hours with headache, days with headache and days with migraine respectively. The mean percentage reduction for secondary efficacy parameters of headache severity index, dose of abortive drugs and number and days of headache leaves was 20%, 22% and 10% respectively.

The reverse trend regarding number of days with sick leaves in our study can be explained on the basis that majority of our patients were house bound females and a fair proportion of unemployed males for whom we had it difficult to demarcate as to what a sick leave actually means for them.

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 favor of lisinopril, thus retaining the statistical significance (p=.000) for all parameters.

These results are well in accordance with the study results by Herald Schreder et al wherein a mean % reduction of 15%, 16% and 22% were reported for hours with headache, days with headache and days with migraine respectively. Secondary efficacy parameters were not analyzed in that study.

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=.000), 1.84 for days with headache (p=0.004), 1.82 for days with migraine(p=.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. The results of Herald Schreder et al were 34%, 30%, 29% respectively for first three parameters.

To compare the efficacy of different drugs reliably, direct comparisons in a single study are needed, So as already discussed the results of our study cannot be compared with those reported for the prophylactic drugs, in the existing literature because of different study designs and different efficacy parameters. Only one of the efficacy parameters in our study i.e., headache severity index can be compared to the results of a metaanalytic study with propranolol which included multiple design studies. The meta-analysis has shown a reduction of 33% for the parameter. Our study shows an improvement of 17% for the same parameter. The design of our study and its being single centered makes this 17% improvement, more promising and meaningful.

In another recent, similar related study with candesarten (Angiotensin II receptor blocker) in the prophylaxis of migraine, the efficacy parameters have been at par with those of our study [16].

This study reveals migraine to be a common ailment more so in the females, with common migraine dominating. Males and urban residents present for treatment earlier as compared to their counterparts.

Thisstudy favors lisinopril 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.

Summary and Conclusion

1. Lisinopril has a significant prophylactic role in migraine.
2. Lisinopril is a safe and well tolerated drug with fewer adverse effects and contraindications.

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