Efficacy Of Felodipine In Hypertensive Patients

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Summary:

Thirtytwo patients were put on calcium channel blocker felodipine, a dihydropyridine derivative, for twelve weeks, after two weeks on placebo treatment, either alone or in combination with other antihypertensive drugs. Mean sitting systolic pressure decreased from 168±3.1 mmHg to 138.5±2.18 mmHg while sitting diastolic pressure decreased from 105±0.8 mmHg to 89±1.06 mmHg. Mean standing systolic pressure decreased from 162±3.2 mmHg to 141±3.4 mmHg and mean standing diastolic pressure decreased from 107±0.9 mmHg to 92±1.4 mmHg. Mean arterial pressure decreased from 125 mmHg to 108 mmHg. Mean pulse rate in sitting position decreased from 94/min to 89/min while drop in mean standing pulse rate was from 103/min to 98/min. There was not much change in pulse rate. Laboratory results remained almost the same before and after treatment. Felodipine was found effective in decreasing blood pressure either alone or in combination with other drugs.

Introduction:

Vasodilators are used commonly as first line of treatment in patients with established hypertension as peripheral vascular resistance is usually increased in these patients. Felodipine, a dihydropyridine derivative, structurally related to nifidepine, inhibits vascular smooth muscle contractile activity. Felodipine has shown more pronounced selectivity on vascular smooth muscles than on heart muscles[1,2,5,8]. This drug exerts its vasodilating effect partly by interaction with intracelluler calcium utilization. In therapeutic concentrations felodipine interact with intracelluler calcium binding proteins rather than inhibition of calcium influx across the potential operated channels[10]. Felodi-pine has been found effective as monotherapy or in combination with other drugs in patients with mild to moderate hypertension[3,4,5].

Felodipine is completely and rapidly absorbed from the gastrointestinal tract when administered as on oral solution[6]. It is extensively distributed to the extravascular sites. It is excreted as metabolites in the urine. Some accumulation of felodipine takes place during long term treatment[6]. Felodipine possesses diuretic effect also which counteract the salt and water retention effect of many other potent vasodilators[7]. Felodipine directly inhibits renal tubular reabsorption of water, sodium and potassium[11].

The aim of this study was to investigate the efficacy and tolerability of felodipine (as monotherapy or as combined therapy with other antihypertensive drugs) in hypertensive patients.

TABLE NO. 1

STUDY DESIGN

Wash out period	one week
Placebo period	two weeks
Active drug treatment period	twelve weeks
On 5mg of active drug	two weeks
On 10mg of active drug	two weeks
Addition of Metoprolol	after 4 weeks

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Patients and Method:

Thirtytwo patients (21 females and 11 males) with mild to moderate hypertension were selected for this study. All patients were put on active treatment for 12 weeks after 2 weeks placebo treatment. Previously untreated patients or newly diagnosed patients were put on 5mg Felodipine/day for 2 weeks. If blood pressure was not controlled then the dose was increased to 10mg/day for another two weeks. After another two weeks 100mg metoprolol was added if blood pressure was still elevated.

TABLE NO. 2

GENERAL INFORMATION

Mean Weight	71.7±2.7 Kg
Mean Height	152.5±3.2 Cm
Mean Age	48.7±1.2 Yrs.
Mean duration of Hypertension	4.7±1.2 Yrs.
Total No. of patients enrolled	32
Withdrawn due to adverse events	3
Excluded due to operation	1
Lost during follow up	1
No. of patients who completed the study	27

The patients whose sitting diastolic pressure was 95 mmHg or greater in spite of taking optimal doses of antihypertensive drugs which he was taking, felodipine was added to the existing antihypertensive medicines or the existing calcium antagonist was replaced with felodipine after two weeks on placebo treatment in these patients combination therapy was given. Previous antihypertensive drugs of the patients in the combined therapy group were kept unchanged throughout the trial period.

Patients visited the antihypertensive clinic fortnightly. Blood pressure was measured with the same mercury sphygmomanometer, by the same observer both in sitting (10 minutes after rest) and standing (2 minutes after standing) position. Phase I and phase V of Kortokoff sounds were taken as systolic and diastolic pressure. A complete history was taken before starting the treatment and physical examination was done during the first and last week of treatment. X-ray chest and ECG were done before starting therapy and at the end of study period. Patients were advised to come fortnightly, on empty stomach between 8.00 A.M. to 11.00 A.M. All adverse events were recorded whether offered spontaneously or elicited after direct questioning. Mean arterial pressure was calculated from the sum of 1/3rd systolic and 2/3rd diastolic pressure. The study was done as an open uncontrolled blind study. Detailed clinical evaluation before starting treatment did not show any secondary cause for the hypertension or any concomitant disorder.

Inclusion Criteria:

Male or female patients above 18 years old. Essential hypertensives either newly diagnosed or uncontrolled with other medicines. Diastolic blood pressure more than 95 mmHg. Informed consent of the patient before starting the treatment.

Exclusion Criteria:

Patient with serious physical illness. Pregnant or lactating women. Women of child bearing potential. All forms of secondary hypertension. Patients with uncompensated cardiac failure, cardiogenic shock or recent (within three months) myocardial infarction. Patients with severe renal impairment. Patients with other severe organic diseases.

TABLE NO. 3

SITTING BLOOD PRESSURE

	Before treatment	After placebo	After treatment
Systolic	162±3.1	167±3.1	139±2.8*mmHg
Diastolic	102±0.0	105±0.8	89±1.0*mmHg
MAP	122	126	105mmHg
Pulse rate	93±1.9	94±1.8	89±1.5/min

*p value <.001

MAP=Mean arterial pressure.

Drop-out Criteria:

Onset of any exclusion criteria. Serious side effects due to active drug. Request for withdrawal from the study by the patient. Patients not visiting the follow up clinic as advised.

Statistical Evaluation:

Statistical evaluation was done for the patients who have completed the study. Two tailed student's test was used to assess the significance of the differences between the mean values. p value >0.05 was considered as insignificant. Results are expressed as mean and standard error of mean.

Efficacy Analysis:

Thirtytwo patients, 21 (65.6%) females and 11 (34.4%) males were admitted for this study. Mean weight before treatment was 71.7±2.71 Kg(range 45-101Kg), mean age was 48.7±1.27 years (range 30-58 years) and mean duration of hypertension was 4.7±1.2 years (range newly diagnosed to 7 years).

Twentyseven patients (84.38%) completed the trial. Three patients were withdrawn from the study because they did not tolerate the drug. One patient was excluded from the study as he developed obstructed inguinal hernia and was operated later on. One patient was lost during follow up so was not included in the statistical analysis.

TABLE NO. 4

STANDING BLOOD PRESSURE

	Before treatment	After placebo	After treatment
Systolic	165±3.9	162±3.2	142±3.4*mmHg
Diastolic	104±1.3	107±0.9	92±1.5*mmHg
MAP	124	125	108mmHg
Pulse rate	100±1.9	103±2.0	98±1.8/min

*p value <.001
MAP=Mean arterial pressure.

Mean sitting systolic pressure before treatment 168±3.1 mmHg was decreased to 138.5±2.18 mmHg after 12 weeks treatment. Sitting diastolic pressure decreased from 105±0.8 mmHg to 89±1.06 mmHg. Mean standing systolic pressure decreased from 162±3.2 mmHg to 141±3.4 mmHg and mean standing diastolic pressure decreased from 107±0.9 mmHg to 92±1.4 mmHg.

Mean arterial pressure in sitting position decreased from 126 mmHg to 105 mmHg. While standing arterial pressure decreased from 125 mmHg to 108 mmHg.

Mean pulse rate in sitting position decreased from 94/min to 89/min while drop in mean standing pulse rate was from 103/min to 98/min.

Ankle circumference was increased in both the legs in some patients but the increase was not significant statistically. This increase was not correlated with a simultaneous increase in weight as individual and mean body weight remained unchanged during the trial.

At the end of study 14 patients were taking 5 mg of felodipine, 4 patients were taking 10 mg of felodipine, 3 patients were taking 10 mg of felodipine and 100 mg of metoprolol, 1 patient was taking 10 mg of felodipine and 10 mg of enalapril, 2 patients were taking 10 mg of felodipine and 75 mg of captopril, 1 patient was taking 10 mg of felodipine and tab. moducren, 1 patient was taking 10 mg of felodipine and 5 mg of lisinopril and 1 patient was taking 5 mg of felodipine and 100 mg of metoprolol as this patient did not tolerate 10 mg felodipine.

Laboratory Results:

No statistically significant difference was observed for haemoglobin and other biochemical tests like cholesterol, triglycerides, HDL, LDL, urea, creatinine, uric acid, serum electrolytes etc. before and after treatment. There was no change in 24 hours urinary protein excretion after three months treatment. X-ray chest and ECG also remained the same after this time period.

Adverse Events:

Palpitation, flushing, headache, lethargy, itch-

ing, dizziness, ankle swelling and distaste in the mouth were the main complaints observed in these patients. These adverse events have been observed by others also[3,4,8]. Three patients were withdrawn from the study treatment as they did not tolerate the drug. These patients developed urticaria, flushing, dizziness and severe headache after taking the first dose. These patients have the same effects when half of the dose was given. No patient had postural hypotension or tachycardia. No tachyphylaxis was observed.

TABLE NO. 5

LABORATORY RESULTS

	BEFORE TREATMENT	AFTER TREATMENT
Hb. mg dl	13.2±0.2	13.5±0.2
S. Bilirubin mg/dl	0.6±0.01	0.5±0.01
SGPT i.u.	25.8±2.5	33.9±3.2
S.G.O.T. i.u.	23.1±2.2	29.8±3.0
S. Cholesterol	192±4.2	201±6.4
S. Triglycerides mg/dl	193±19.1	227±17.8
HDL	34.9±0.9	40±3.9
LDL	123.7±3.9	124±6.9
Blood Urea mg/dl	28.5±0.9	26±1.2
S. Creatinine mg/dl	0.9±0.02	0.8±0.03
S. Uric Acid mg/dl	6±0.2	8.6±1.8
S. Sodium mEq/l	142±0.9	140±0.9
S. Potassium mEq/l	3.9±0.08	4.1±0.09
S. Chloride meq/l	97.4±0.7	95.8±0.4
S. Alkaline Phosphatase i.u.	265±12	274±16
Blood Sugar mg/dl	113±13.5	122±11.4

Discussion:

Beta blockers, or diuretics or methyldopa were used for a long time as the 1st drug of choice for treatment of hypertension. But now the trend is changing. Other drugs like vasodilators are in use now, some vasodilators have some limitations like hydralzine may cause systemic lupus erythmatosus. Prazosin dilates both arteries and veins which may cause orthostatic hypotension.

The aim of our study was to observe the efficacy of felodipine as monotherapy and in combination therapy with other drugs in lowering the blood pressure both in sitting and standing position. We also observed the tolerability of this drug in our population by observing the side effects within this short period. This drug was also compared with placebo.

Patients with essential hypertension have to take treatment for an indefinite period. So a drug is advisable which has minimum side effects and has good tolerance and compliance. Patients non compliance with antihypertensive therapy is a major obstacle in achieving an effective control of blood pressure.

In the present study we have found that felodipine decreases blood pressure smoothly alone or in combination with other antihypertensive drugs during twelve weeks time. In three patients the drug was omitted due to intolerance while in another the dose was reduced to 5 mg because of intolerance to 10 mg felodipine.

TABLE NO. 6

ADVERSE EVENTS

	Placebo	Active treatment
Distaste mouth	1	2
Itching	1	5
Nausea	2	0
Loose Motion	2	0
General aches	1	2
Palpitation	0	5
Headache	0	4
Flushing	0	4
Urticaria	0	2
Diuresis	0	3
Sinking heart	0	1
Pain legs	0	2
Constipation	0	3
Dizziness	0	3
Ankle oedema	0	4

Use of vasodilators is often associated with ankle swelling due to salt and water retention. But felodipine has natriuretic effect[11,12] which appears to be sufficient to counteract the expected fluid retention. It is said that the ankle oedema is caused by pronounced precapillary vasodilatation and increased capillary filtration[7,8] than fluid accumulation. This is also confirmed by the fact that the body weight remained unchanged after treatment.

Conclusion:

Felodipine decreased the supine diastolic blood pressure below 90 mmHg in 79.3% of patients either alone or in combination with other drugs. Three patients were excluded from the study due to intolerance to drug while in one patient the dose was decreased to 5 mg/day. Most of the side effects were transient and disappeared with the passage of time. Major side effects were palpitation, headache, sinking of the heart, pain in the legs, itching and dizziness. Felodipine can be used safely as monotherapy or in combination with other drugs in patients with mild to moderate hyertension.

TABLE NO. 7

DRUG TREATMENT AT THE END OF STUDY

DRUG	PATIENTS NO.
On 5 mg Felodipine	14
On 10 mg Felodipine	4
On 10 mg Felodipine and 100 mg Metoprolol	3
On 10 mg Felodipine and 10 mg Enalapril	1
On 10 mg Felodipine and 75 mg Sartorial	2
On 10 mg Felodipine and Tab. Nocturne	1
On 10 mg Felodipine and 5 mg Lisinopril	1
On 5 mg Felodipine and 100 mg Metoprolol	1

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