

**COMPARATIVE STUDY OF EFFICACY OF ANTIHYPERTENSIVE AGENTS -  
METHYLDOPA, PRAZOSIN, HYDRALLAZINE SINGLY AND  
HYDRALLAZINE AND FRUSEMIDE IN COMBINATION**

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**ABSTRACT:**

In a single blind limited clinical evaluation the relative efficacy of methyldopa, prazosin hydrochloride, hydrallazine singly and hydrallazine and frusemide in combination to reduce the blood pressure in essential hypertension was carried out. Out of the total 68 cases, 47 (69%) completed the trail in an eight weeks follow up period. Methyldopa as a single agent was found to be more effective in reducing systoloc blood pressure significantly ( $p < .001$ ). Hydrallazine and frusemide in combination was more effective in reducing the diastolic blood pressure ( $P < .001$ ) and also mean blood pressure ( $P < .001$ ). Besides, all the four drugs reduced both systolic, diastolic and mean pressure in all the patients significantly ( $P < .02$  to  $.01$ ).

**INTRODUCTION:**

At present many potent drugs are available for the treatment of essential hypertension. The drugs differ widely in their mode of action and the sphere of usefulness. Availability of these drugs has not made the problem of treatment solved because there is no single universally accepted drug for the treatment of all hypertensives <sup>(1)</sup>. Recent trend suggests combination of antihypertensive drug therapy. Methyldopa in combination with a diuretic are gaining popularity. Combination of betablocker with a vasodilator as for example hydrallazine or prazosin is particularly useful as they counteract the side effects of each other. <sup>(2)</sup>.

Methyldopa, prazosin hydrochloride, hydrallazine are all available in our country. Still now, vast majority of the patients of our country are being treated by one or the other of these drugs either single or in combination. So, it was felt justified to undertake a comparative study of efficacy of these drugs- Methyldopa, prazosin hydrochloride and hydrallazine singly, and hydrallazine + Frusemide in combination in different groups of people. Further more, such a comparative study was not done in our country.

## PATIENTS AND METHODS

All the patients of essential hypertension who attended the general hospital Barisal and gave consent to participate in this study were included. Sixty eight (68) adult male and female whose diastolic blood pressure was above 95 mm Hg were selected for this study.

Detailed history and physical examination were done in each case and all available investigations were performed including X-Ray chest and 12 lead E C G recordings. Investigations were repeated as and when felt necessary.

For the purpose of this study patients were divided into four groups (Gr-A, B, C, D,) according to the following sequence. The first patient was placed in group A, the next patient in group B, the next in group C and the fourth in group D. Again the fifth into Gr A and so on. Patients of Gr-A, Gr-B, Gr-C and Gr-D were treated by methyldopa, prazosine hydrochloride, hydrallazine and hydrallazine and frusemide combination respectively. All the patients were subjected to observation without treatment for one week. Antihypertensive drugs were omitted one week before the trial in cases where the patient took antihypertensive drugs prior to the commencement of the trial. Then all these patients were kept on placebo treatment for another one week.

The study was single blind. After keeping the patient on placebo treatment without any antihypertensive treatment for one week, the antihypertensive treatment were started as per above schedule. The initial dose of methyldopa was 250 mg 2 to 3 times daily. If control of blood pressure was not achieved the dose of methyldopa was increased to a maximum of 500 mg three times daily, the increment being 250 mg on every third day. Prazosine was started with the initial dose of 0.5 mg daily to a maximum dose of 6 mg three times daily. Hydrallazine was tried with the starting dose of 25 mg daily to a maximum of 100 mg daily. In hydrallazine + frusemide group (Gr-D) the initial dose were 25 mg and 20 mg respectively and the maximum dose were 100 mg and 40 mg respectively.

Blood pressure was measured both in supine and erect position twice daily at 8 AM and 8 PM. The measurement done by a fixed person with a particular sphygmomanometer. Heart rate was also recorded. Treatment was continued till the control of blood pressure was achieved. Patients were allowed to go home with an appropriate advice regarding the maintenance dose. Patients were instructed to come every week for follow up for period of two months.

## RESULTS AND OBSERVATIONS :

Initially a total of 68 cases were included in our study. Of them 47 cases completed the study schedule. Twenty one cases were excluded from the study because of various reasons. Out of these 21 cases, 15 cases didnot report for follow up, in four patients blood pressure was controlled only with placebo and no subsequent treatment was needed, two patients were dropped because of unsatisfactory controll of blood pressure. The final analysis of the results were made on basis of these 47 cases.



Of the total 47 cases 28 (59.6%) were male and 19 (40.4%) were female. The mean age of the series was 51 yrs with an age range of 23 - 75 yrs. The following table (Table-1) shows the age and sex distribution of the different groups of the patients.

Group	Drug used	Male	Female	Total	Mean age (range)
A	Methyl dopa	8	5	13	48.3 yrs (23-70 yrs)
B	Prazosine	8	5	13	49.5 yrs (29-65 yrs)
C	Hydrallazine	6	5	11	52.8 yrs (28-70 yrs)
D	Hydrallazine + Frusemide	6	4	10	57.1 yrs (38-75 yrs)

Table -1, showing the age and sex distribution of the different treatment groups of the 47 cases of hypertension.

Majority (28) of cases (59.5%) of the series had mild hypertension. 15 cases (31.9%) had moderate hypertension and 4 cases (8.5%) had severe hypertension.

#### Results of treatment by placebo.

As stated earlier the patients of all the groups were subjected to placebo treatment before starting antihypertensive therapy. It was found that only four cases of the total patients became normotensive by placebo treatment. In 47 cases the placebo did not lower the blood pressure significantly. The results of treatment by placebo in different groups of patients are given in tables : II, III, IV and V.

#### Results of antihypertensive treatment

All the drugs used in this study were found effective in reducing the systolic, diastolic and mean blood pressure. And also the maintenance therapy were found effective in keeping the blood pressures stable in the eight weeks follow up period. Methyl dopa was found to be more effective in reducing systolic blood pressure ( $P < 0.001$ ) than other agents while hydrallazine and frusemide was found more effective in reducing the diastolic blood pressure ( $P < .001$ ) than the other drugs. The following tables (Table-II, III, IV & V) show this reduction of blood pressure in all the treatment groups.

Methyl dopa reduced supine systolic, diastolic and mean blood pressure from 204.2 to 175.5 mmHg ( $P < .001$ ), 115.6 to 101.8 mm Hg ( $P < 0.05$ ) and 145.2 to 130.6 mmHg ( $P < 0.02$ ) respectively. Prazosin reduced the supine systolic diastolic and mean blood pressure from 190.2 to 169.4 mm Hg ( $P < 0.01$ ) 114.2 to 99.2 ( $P < 0.05$ ) and 143.2 to 128.4 mmHg ( $P < 0.5$ ) respectively. Hydrallazine reduced the supine systolic diastolic and mean blood pressure from 200.2 to 188.6 mmHg ( $P < 0.5$ ), 115.3 to 99.5 mmHg ( $P < 0.02$ ) and 143.8 to 123.5 mmHg ( $P < 0.01$ ) respectively. Hydrallazine and frusemide combination reduced the supine systolic, diastolic and mean blood pressure from 212.3 to 189.5 mmHg ( $P < 0.01$ ) 117.4 to 109.3 mmHg ( $P < 0.001$ ) and 147.4 to 118.3 mmHg ( $P < 0.001$ ) respectively. The blood pressures in erect posture were also reduced in a similar manner.

Table-II: Arithmetic mean arterial blood pressure with placebo and methyl dopa treatment (n=13)

Supine blood pressure	Before placebo in mmHg ( $\pm$ SEM)	After placebo in mmHg ( $\pm$ SEM)	Before Methyldopa in mm Hg ( $\pm$ SEM)	After Methyldopa in mmHg ( $\pm$ SEM)
Systolic	212.4 (5.1)	204.3 (NS) (4.9)	204.2 (4.7)	175.5**** (4.5)
Diastolic	112.3 (4.6)	115.6 (NS) (4.2)	115.6 (4.3)	101.8* (3.9)
Mean	138.4 (4.1)	145.2 (NS) (3.8)	145.2 (3.8)	130.6** (3.2)
Erect Blood pressure				
Systolic	210.3 (4.8)	200.2 (NS) (5.2)	190.7 (4.7)	163.2 **** (4.3)
Diastolic	113.3 (4.5)	115.5 (NS) (4.1)	110.3 (4.2)	98.2* (3.7)
Mean	133.2 (4.2)	142.3 (NS) (4.6)	140.7 (3.5)	128.6* (3.7)

\* P = < 0.05

\*\* P = < 0.02

\*\*\*\* P = < 0.001

NS = Not significant

Table-III : Arithmetic mean of arterial blood pressure with placebo and prazosin HCl treatment (n=13)

Supine blood pressure	Before placebo in mmHg ( $\pm$ SEM)	After placebo in mmHg ( $\pm$ SEM)	Before prazosin in mm Hg ( $\pm$ SEM)	After prazosin in mmHg ( $\pm$ SEM)
Systolic	198.5 (3.9)	190.2 (NS) (4.8)	190.2 (4.8)	169.4**** (4.3)
Diastolic	116.6 (4.1)	114.2 (NS) (4.5)	114.2 (4.5)	99.2 * (5.3)
Mean	138.4 (4.1)	145.2 (NS) (3.8)	143.2 (5.2)	128.4 * (4.6)
Erect Blood pressure				
Systolic	190.3 (4.1)	187.2 (NS) (3.8)	185.1 (5.1)	160.3 *** (4.8)
Diastolic	116.2 (4.6)	117.4 (NS) (4.1)	112.2 (4.1)	90.6 *** (5.2)
Mean	152.4 (5.5)	150.4 (NS) (4.7)	140.3 (5.6)	118.4** (4.8)



\* P = &lt; 0.05

\*\*\* P = &lt; 0.01

NS = Not significant

Table- IV : Arithmetic mean arterial blood pressure with placebo and hydrallazine treatment

Supine blood pressure	Before placebo in mmHg ( $\pm$ SEM)	After placebo in mmHg ( $\pm$ SEM)	Before hydrallazine in mm Hg ( $\pm$ SEM)	After hydrallazine in mmHg ( $\pm$ SEM)
Systolic	206.7 (4.1)	202.2 (NS) (3.8)	200.2 (3.8)	188.6 * (3.2)
Diastolic	113.5 (4.7)	115.3 (NS) (3.8)	115.3 (3.8)	99.5 ** (4.5)
Mean	142.9 (4.9)	143.8 (NS) (5.1)	143.8 (5.1)	123.5*** (2.9)
Erect Blood pressure				
Systolic	198.3 (4.1)	202.2 (NS) (3.7)	196.2 (3.6)	180.1 *** (3.5)
Diastolic	113.4 (5.2)	112.5 (NS) (4.1)	114.3 (4.1)	92.5** (4.2)
Mean	142.3 (4.9)	145.5 (NS) (3.8)	138.2 (4.6)	116.4** (3.8)

\* P = &lt; 0.05

\*\* P = &lt; 0.02

\*\*\* P = &lt; 0.01

\*\*\*\* P = &lt; 0.001

NS = Not significant

Table V : Arithmetic mean arterial blood pressure with placebo and hydrallazine-frusemide combination treatment (n=10)

Supine blood pressure	Before placebo in mmHg (+ SEM)	After placebo in mmHg (+ SEM)	Before hydrallazine + Frusemide in mm Hg ( $\pm$ SEM)	After hydrallazine + Frusemide in mmHg ( $\pm$ SEM)
Systolic blood pressure	221.5 (4.6)	212.3 (NS) (4.8)	212.3 (4.8)	189.4*** (4.2)
Diastolic blood pressure	116.1 (4.5)	117.4 (NS) (4.1)	117.4 (4.1)	93.3 **** (2.9)

Mean blood pressure	152.2 (4.5)	147.4 (NS) (4.6)	147.4 (4.6)	118.3 **** (3.4)
Erect Blood pressure				
Systolic blood pressure	217.4 (4.6)	210.5 (NS) (4.3)	213.4 (4.3)	189.2 *** (4.7)
Diastolic blood pressure	120.6 (4.1)	114.5 (NS) (3.8)	114.4 (4.2)	87.5 **** (2.8)
Mean blood pressure	148.7 (4.1)	157.2 (NS) (5.2)	140.4 (3.8)	108.3 **** (4.1)

\*\*\* P = < 0.01

\*\*\*\* P = < 0.001

NS = Not significant

## DISCUSSION:

A single blind clinical trial was carried out to show the comparative in antihypertensive efficacy of the four commonly used drugs singly and one combination. The results reveal statistically significant reduction of blood pressure by all the drugs in all the groups. This was true both for erect and supine blood pressure. This is in agreement with other similar studies (3.4, 5.6). The doses were similar to those of the present study.

The study also revealed that methyldopa is more effective in reducing the systolic than diastolic blood pressure. While hydrallazine were efficient in reducing the diastolic blood pressure. It is very difficult to explain the above findings. This may be related to reduction of the cardiac out put by methyldopa. Similarly, perhaps, hydrallazine and frusemide decreases the peripheral resistance in a larger scale than the other agents and thus reduce the diastolic blood pressure significantly more than the other agents. However, the exact interactions of these agents with those of the factors responsible for normal maintenance as well as genesis of hypertension are yet to be worked out. As methyldopa produces pronounced fall in systolic blood pressure so it may be useful in patients with marked systolic hypertension. Like wise frusemide and hydrallazine may be a good combination in the treatment of patients with marked diastolic blood pressure.

It is an established fact that none the drugs introduced upto the present time can reduce blood pressure in all the patients and few people respond yet to placebo (7). In our series four patients responded to placebo. And also it is not surprising two of our patients, in spite of using all the drugs, blood pressure could not be controlled.

Though the number of patients in each group were not sufficient enough to draw a definite conclusion. It may be deduced that the therapeutic efficacy of all the four drugs were similar with the exception of methyldopa which has greater efficacy in reducing systolic blood pressure and hydrallazine and frusemide in reducing diastolic blood pressure.

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