EFFICACY ON MONOTHERAPY VS COMBINATION THERAPY IN HYPERTENSIVE PATIENTS: A COMPARATIVE STUDY

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ABSTRACT

Background: Little is known about the relative effectiveness of antihypertensive medications or combinations. The management of hypertension patients will be improved by identifying the most efficient ones and the patient's features related with the best performance of medications.

Aim and objective:The purpose of our study is to examine the effectiveness of antihypertensive medications when used in immunotherapy and combination treatment. Another goal is to evaluate the blood pressure (BP) reductions attributable to antihypertensive medications and discover traits linked with BP reduction.

Measurements and results Systolic and diastolic blood pressure (SBP) mean reductions brought on by single or combined therapies.

Methods and materials: Demographic and baseline characteristics were summarized using descriptive statistics of the methodological quality and the characteristics of the populations studied were performed. Blood pressure recordings from various hospital visits of the patient were collected and their mean and standard deviation values were calculated and noted quantitatively. Comparisons of categorical data were made using the Mood's median test. Significance was defined as P<.05. Comparison among groups was performed using the point- biserial correlation coefficient test. The drugs given in monotherapy were Losartan, Amlodipine, Valsartan, and Hydrochlorothiazide and in combination therapy were Losartan/ Hydrochlorothiazide, Losartan/Amlodipine, Amlodipine/Telmisartan, and Valsartan/ Hydrochlorothiazide.

Results: Valsartan/ Hydrochlorothiazide combination showed to be more effective with a mean reduction of SBP (-26.6□23.5mmHg) and DBP (-15□11.1mmHg) respectively when compared to other combinations.

Conclusion: Combination therapy was more effective in treating hypertension than monotherapy.

Keywords: Systolic blood pressure, diastolic blood pressure, monotherapy, combination therapy, antihypertensive drugs.

INTRODUCTION

Globally widespread, hypertension is a disorder that raises the risk of mortality and treatable illness. It continues to be a prevalent and critical issue, significantly contributing to the most prevalent causes of illness and mortality in emerging nations. 2. The first line of treatment for lowering blood pressure is monotherapy. 8 But some people can regulate their blood pressure and lower it to levels that are advised by guidelines by using just one drug. 9 Combination treatment is a different method of treating hypertension.

If low-dose monotherapy is chosen and blood pressure control is not achieved, the next step is to switch to a low dose of a different agent or to increase the previous agent to full dose. Monotherapy is the standard initial treatment for reducing blood pressure in most patients with hypertension, moving to combination therapy (2 or more drugs from different classes) when stepwise increases in the dose of 1 drug fail to achieve the desired decrease in blood pressure.[10,11,12,13] Combinationtherapy may be used according to the circumstances if target blood pressure values are not achieved: systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg in adults and <130/80 in special populations.[14]

NEED FOR STUDY:

- To enhance the clinical outcomes with antihypertensive drugs in treating hypertension as it is the most common risk factor throughout the world.
- To assess the patient's knowledge and awareness about hypertension and adherence to antihypertensive medication among hypertensive patients with validated data collection form and questionnaires in a tertiary care hospital.
- To assess the attitudes of hypertensive patients, especially related to drugs in reducing SBP and DBP.
- To conclude the better therapy among hypertensive patients receiving mono and combination therapies.
- To optimize the most effective combination in reducing blood pressure.
- To search the relation between knowledge about hypertension, socio-demographic characteristics and obtaining controlled BP levels among patients diagnosed with hypertension.

MATERIALS AND METHODS FOR METHODOLOGY:

Study Design: A Panel Study

Study site: Outpatient Department of General Medicine, VIMS.

Sampling Technique: Stratified Random Sampling

Study population:

INCLUSION CRITERIA

- Patients of age group 35-60 years.
- Systolic blood pressure: >140mmHg.
- Diastolic blood pressure: >90mmHg.
- Co-morbid conditions: Diabetes.
- Documented evidence of disease must be there.

EXCLUSION CRITERIA

- More than 10 years of known hypertension.
- Age <35 years.
- Pregnant women.
- Lactating women.
- Patients who missed to follow up.

Sample size:

Estimated number of patients: 100 patients [GROUP A: 50 patients (with monotherapy); GROUP B: 50 patients (with combination therapy)].

Obtained number of patients (After exclusion criteria): 60 patients [GROUP A: 29 patients (with monotherapy); GROUP B: 31 patients (with combination therapy)].

Study instruments: Blood pressure was assessed after the participant was in a seated position for at least 5minutes. Blood pressure was measured with an automatic measurement device 3 times at 1 to the 2-minute interval and a mean of 3 measurements was calculated.

Data Collection: The data collection was done in three phases. In the first phase, demographic data (name, age, sex, height, weight, contact number and address) was collected from patients and case sheets if necessary. In the second phase clinical characteristics [blood pressure (B.P), duration of hypertension] was collected from case sheets. In the third phase, information about their medications was collected and the patients are then categorized into two groups. A detailed case pro-forma for data collection was prepared.

Study Procedure:

1. Permission from the ethics committee was obtained
2. Enlisting patients into the study as per the directions of the doctor, and as per inclusion criteria.

3. Patient demographic details and clinical data were collected from the case sheets.
4. Patient's prescription was then assessed and they were categorized into two groups i.e., GROUP-A and GROUP-B.
5. GROUP-A and GROUP-B patients were followed every month.
6. The results of both the groups were compared and documented.

Data Analysis:

Demographic and baseline characteristics were summarized using descriptive statistics of the methodological quality and the characteristics of the populations studied were performed. Blood pressure recordings from various hospital visits (i.e., visit 1, 2, 3 respectively) of the patient werecollected and their mean and standard deviation values were calculated and noted quantitatively. Comparisons of categoric data were made using Mood's median, a nonparametric test to measurethe equality of medians from two populations. Comparison among groups was performed using the point-biserial correlation coefficient test in which one variable (e.g. *X*) is dichotomous. The level of statistical significance was considered at $p<0.05$

RESULTS

Table 1: Socio-demographic details of patients

S.NO	CHARACTERISTICS	MONOTHERAPY	COMBINATION THERAPY
1	AGE (in years)		
	35-40	2	2
	40-45	1	1
	45-50	4	6
	50-55	4	4
	55-60	18	18
2	GENDER		
	Male	15	19
	Female	14	12
3	AREA OF RESIDENCE		
	Rural	1	0
	Urban	28	31
4	OCCUPATION		
	Employed	10	6
	Unemployed	19	25
5	FAMILY HISTORY		
	Significant	10	10

	Not significant	19	21
6	SMOKING HISTORY		
	Smokers	8	7
	Non-Smokers	21	24
7	ALCOHOL HISTORY		
	Alcoholic	9	7
	Non-Alcoholic	20	24
8	DURATION OF HTN		
	<5	24	25
	>5	5	6
9	DIABETES		
	Diabetic	12	7
	Non-Diabetic	17	24

Table 2: Distribution of patients based on the type of therapy

S.NO	**TYPE OF THERAPY**	**FREQUENCY**
A	**MONOTHERAPY**	**29**
1	LOSARTAN	5
2	AMLODIPINE	13
3	HYDROCHLOROTHIAZIDE	7
4	VALSARTAN	4
B	**COMBINATION THERAPY**	**31**
1	LOSARTAN+AMLODIPINE	10
2	VALSARTAN+HYDROCHLORTHIAZIDE	6
3	LOSARTAN+HYDROCHLORTHIAZIDE	6
4	AMLODIPINE+TELMISARTAN	9

Note: The doses of the following drugs are as follows: Losartan-50mg, Amlodipine-5mg, Hydrochlorothiazide-12.5mg & 25mg, Valsartan-40mg.

Table 3: Blood pressure values of patients based on the type of therapy at different hospital visits

S.NO	TYPE OF THERAPY	BASELINE		VISIT 1		VISIT 2	
		SBP	DBP	SBP	DBP	SBP	DBP
1	Mono therapy	158.5±14.2	94.7±8.6	153.2±9.21	92.06±8.14	148.62±10.6	88.27±6.33
2	Combination therapy	165.6±17.8	95.8±7.08	155±9.42	88.06±6.43	142.25±8.69	82.25±4.89

Table 4: Blood pressure values of patients receiving monotherapy at different hospitalvisits

S.NO	MONO THERAPY	BASELINE		VISIT 1		VISIT 2	
		SBP	DBP	SBP	DBP	SBP	DBP
1	Amlodipine	163.4±14.3	97.6±7.9	156.9±8.2	96.1±5.6	151.9±8.8	92.3±5.4
2	Hydro chlorothiazide	156.71±8.5	91±8.4	151.4±4.4	90.7±7.7	148.5±10.2	84.2±4.9
3	Losartan	150±10.9	94±4.8	146±4.8	90±6.3	143±4	88±4
4	Valsartan	156.2±18.4	92.5±10.8	153.75±14.7	83.75±9.6	145±16.5	82.5±4.3

Table 5: Blood Pressure values of patients receiving combination therapy at differenthospital visits

S. N0	COMBINATION THERAPY	BASELINE		VISIT 1		VISIT 2	
		SBP	DBP	SBP	DBP	SBP	DBP
1	Telmisartan+ Amlodipine	162±13.9	96.6±8.1	153.3±8.1	87.7±7.8	142.2±7.8	82.2±4
2	Valsartan± Hydrochlorothiazide	175±28.1	100±57	156.6±12.4	91.6±6.8	148.3±12.1	85±7.6
3	Losartan+ Hydrochlorothiazide	158.3±10.6	91.6±3.7	153.3±7.4	85±5	138.3±3.7	80±0

4	Losartan+ Amlodipine	167.5±12.8	95±6.7	159±8.3	88±4	141±7	82±4

Table 6: Blood pressure reduction of antihypertensive drugs in monotherapy

S.NO	MONOTHERAPY	SBP	DBP
1	Amlodipine	-11.5±11.16	-5.3±6.03
2	Hydrochlorothiazide	-8.14±6.03	-6.7± 4.3
3	Losartan	-7±7.4	-6 ± 4.89
4	Valsartan	-11.25±2.1	-10 ±7.07

Table 7: Blood pressure reduction of antihypertensive drugs in combination therapy

S.NO	COMBINATION THERAPY	SBP	DBP
1	Telmisartan+ Amlodipine	-18.8±12.8	-13.3±4.7
2	Valsartan± Hydrochlorothiazide	-26.6±23.5	-15±11.1
3	Losartan+ Hydrochlorothiazide	-20±10	-11.6±3.7
4	Losartan+ Amlodipine	-26.5±10.5	-12± 6

Table 8: Blood pressure reduction based on the type of therapy.

S.NO	TYPE OF THERAPY	SBP	DBP
1	MONOTHERAPY	-9.8± 8.86	-6.4± 5.8
2	COMBINATION THERAPY	-23.3 ±14.7	-12.2± 7.9

Table 9: Association between the type of therapy and blood pressure

S.NO	VISIT NUMBER	BLOOD PRESSURE	'P' VALUE
1	1	SYSTOLIC	0.02
		DIASTOLIC	0.002

2	2	SYSTOLIC	0.0007
		DIASTOLIC	0.0001

Table 10: Correlation between type of therapy and blood pressure for different groups

S.NO	VISIT NUMBER	BLOOD PRESSURE	'r' VALUE	P-VALUE
1	1	SBP	+0.13	0.15
		DBP	-0.26	0.02
2	2	SBP	-0.31	0.007
		DBP	-0.47	<0.001

In our study, the following data were gathered: social demographic details of the patient, SBP and DBP (mean±SD), an antihypertensive drug, and dose. The total population of 60 patients were included in the study whose characteristics are showninTable1. There is a significant difference between two groups (p<.05) regarding systolic and diastolic function indexes (table 9).

Antihypertensive efficacy of specific antihypertensive drugs used as monotherapy:

Although the decrease in BP was overall similar among the different pharmacological classes (table 3), the specific analysis of the drugs used in monotherapy showed relevant differences (table 4). When considering the BP reduction by drugs on monotherapy at mean doses, we observed that the mean SBP reduction from baseline to week 8 is seen more effective with amlodipine (-11.5□ 11.16 mmHg), Valsartan (-11.25□ 2.1 mmHg), hydrochlorothiazide (-8.14

□6.03 mmHg), losartan (-7□7.4 mmHg).

Regarding the mean DBP reduction from baseline to week 8 is seen more effective with valsartan (-10 □7.07 mmHg) compared to the other drugs hydrochlorothiazide (-6.7□ 4.3 mmHg), losartan (-6 □ 4.89 mmHg), amlodipine (-5.3□6.03 mmHg) respectively.

Antihypertensive efficacy of combination drugs:

The specific analysis of the drugs used in combination therapy showed relevant differences (table 5). The mean SBP reduction of the combination drugs from baseline to week 8 is seen more effective with Valsartan+ Hydrochlorothiazide (-26.6 □ 23.5 mmHg), compared to other drugs Amlodipine (-26.5 □ 10.5 mmHg), Losartan+ Amlodipine (-26.5 □ 10.5 mmHg),

Losartan+ Hydrochlorothiazide (-20 □ 10 mmHg),Telmisartan+ Amlodipine (-18.8 □ 12.8 mmHg), respectively.

The mean DBP reduction is more effective with Valsartan+ Hydrochlorothiazide (-15 □ 11.1 mmHg) compared to other drugs Telmisartan+ Amlodipine (-13.3□ 4.7mmHg), Losartan+ Amlodipine (-12 □ 6 mmHg), Losartan+ Hydrochlorothiazide (-11.6 □ 3.7 mmHg), respectively.

Comparative efficacy of both the drugs:

Although both the therapies had shown the BP reduction, the analysis showed the difference in their efficacies (table 3). Mean changes in DBP and SBP for each treatment group are summarized by using pre-specified comparison and superiority test (table 3). All treatments significantly reduced DBP and SBP from baseline to 8 weeks of treatment (all p<0.05) in table 9.

The mean decrease from baseline to week 8 of SBP/DBP was significantly greater in the combination therapy (-23.3 □14.7/-12.2□ 7.9mmHg) compared to monotherapy (-9.8□ 8.86/-6.4□5.8mmHg).

DISCUSSION:

Our study shows that patients were initiated with four antihypertensive drugs as monotherapy and four as combination therapy. Patients with combination therapy had remarkably great reductions in blood pressure at follow-up. These results are consistent with those stated by *Michael R. Bronsert et al.,* who observed that primary care patients initiated on an FDC had considerably larger reductions in blood pressure and higher goal attainment rates at follow-up than patients initiated on monotherapy. These results confirm those observed in short-term, randomized clinical efficacy studies and 2 recent observational studies, all of which showed that patients initiated on an FDC obtain better control of their blood pressure than patients initiated on monotherapy alone.[27, 28, 29, 30]

Valsartan/Hydrochlorothiazide is the combination leading to great reductions in blood pressure.Moreover, our results have important clinical implications since the complementary use of agents from different classes, such as in the Amlodipine, Hydrochlorothiazide, Losartan and Valsartan group on monotherapy and in combination with Telmisartan/Amlodipine, Amlodipine/Valsartan, Valsartan/Hydrochlorothiazide, Losartan/Amlodipine.

Combination therapy with Valsartan/Hydrochlorothiazide produced greater reductions in SBP and DBP from baseline to week 8. At baseline, mean SBP and DBP were found to be 158□10.6 and 91.6□3.7mmHg to week 8, mean SBP and DBP 138.3□3.7 and 80□0 respectively in the

Valsartan/Hydrochlorothiazide group, similar to the study of *Daniel A. Dupreza et al.,* in which a sub-study (n=108) subjects were taken and treatment initiated with Valsartan/Hydrochlorothiazide lowered BP more effectively than either monotherapy throughoutthe daytime, night-time, and 24-h monitoring periods, as well as during the last 4 and 6-h dosing periods. At baseline, mean SBP/DBP±SD was 141.1±10.7/76.5±9.3mmHg in the Valsartan/Hydrochlorothiazide group, 142.2±9.3/ 78.7±7.5mmHg in the Hydrochlorothiazide group, and 142.2±10.6/78.3±8.2mmHg in the Valsartan group.

In our analysis of data from over 1300 patients, greater BP reductions were observed with combination therapy of Valsartan/HCTZ than with monotherapy at all baseline BP values. As would be expected, the higher-dose combination of Valsartan/HCTZ (320mg/25mg) was more effective than the lower dose combination (160mg/12.5mg).[32]

Similarly, another combination therapy with Losartan/Amlodipine also produced reductions in SBP and DBP from baseline to week 8. At baseline, mean SBP and DBP were found to be 167.5□12.8 and 95□6.7 to week 8, mean SBP and DBP 141□7 and 82□4 respectively in the Losartan/Amlodipine group but the reduction of blood pressures by this combination was found to be less when compared with Valsartan/Hydrochlorothiazide combination. This was similar to the study of *Soon Yong Suh et al.,*In which patients who did not achieve a DBP of less than 90 mm Hg on Losartan 100mg showed significantly showed greater improvement in BP when switched to the combination. Losartan/Amlodipine combination was found to be well tolerated and efficacious for the achievement of adequate BP control in HTN patients. Response rate in terms of SBP greater than 20 mm Hg and DBP greater than 10 mm Hg was significantly greater at 8 weeks in Losartan/Amlodipine group. These findings suggest that Losartan/Amlodipine group has a more significant effect and also reduces the more significant reduction in BP.[33]

Telmisartan/Amlodipine combination therapy also produced reductions in SBP and DBP from baseline to week 8. At baseline, mean SBP and DBP were found to be 162□13.9 and 96.6□8.1 to week 8, mean SBP and DBP 142.2□7.8 and 82.2□4.1 respectively in the Telmisartan/Amlodipine group as stated by *William B. White et al.,*in his study where Combination therapies of Telmisartan and Amlodipine lowered 24-h BP to a larger

extent than the corresponding monotherapies at all doses. Mean reductions from baseline in 24-h BP for the combination of the highest doses of Telmisartan (80mg) and Amlodipine (10mg) were –22.4/–14.6 versus –11.9/– 6.9mmHg for Amlodipine (10mg) and –11.0/–6.9mmHg for Telmisartan (80mg) (P<0.0001 for each comparison). In addition, BP response and control rates (24-h BP <130/80mmHg) were significantly higher with the combination therapy versus the monotherapy groups.[39]

Combination therapy with Amlodipine/Valsartan also produced reductions in SBP and DBP from baseline to week 8. At baseline, mean SBP and DBP were found to be 175□28.1 and 100□57 to week 8, mean SBP and DBP 148.3□12.1 and 85□7.6 respectively in the Amlodipine/Valsartan group as stated by *JM Flack et al.,* in his study where amlodipine/valsartan controlled more patients to the BP goal 140/90mmHg. The BP lowering and control rates were greater in Amlodipine/Valsartan than with Amlodipine monotherapy. In addition, the combination therapy was more effective than Amlodipine in the reduction of MSSBP from baseline in many subgroups analysed, including older adults (X65 years), those with isolated systolic hypertension, overweight and obese patients, and patients with diabetes. In conclusion, in this study of black patients with stage 2 hypertension, combination therapy with Amlodipine/Valsartan lowered BP more effectively than Amlodipine alone with a favourable safety profile comparable to Amlodipine monotherapy.[40]

Yan Lva et al., stated that the combination treatment generated significantly greater reductions for the mean ambulatory SBP and DBP during the full 24 hours (SBP 4.24, 95% CI: 6.82–1.67, P=0.001; DBP 2.23, 95% CI: 3.73–0.69, P=0.004).[44, 45, 40,] Five trials[46, 47, 48, 49, 50] reported the hypertension therapeutic control rate (SBP <140, DBP <90). Among these studies, the combination treatment had a higher therapeutic rate (RR: 1.36, 95% CI: 1.07–1.73, P=0.013). The combination therapy was associated with better clinical SBP and DBP control when compared with monotherapy, which is similar to our study where combination treatment generated greater blood pressure reductions for both SBP and DBP.[51]

CONCLUSION

Over a period of 4-8 weeks, the average reductions in SBP appeared most markedly with amlodipine (-11.5□11.16 mmHg), which reduced SBP to a greater extent than any of the other drugs evaluated, and reductions in DBP was most effectively seen with valsartan (-10 □7.07 mmHg) in monotherapy. The reduction in SBP and DBP at 8 weeks was significantly greater in patients treated with the combination therapies compared with the respective monotherapies for all specified comparisons. Averagely weighted reductions in SBP (-26.6 □ 23.5 mmHg) and DBP (-15 □ 11.1 mmHg) were most markedly seen with Valsartan/Hydrochlorothiazide than any of the other combinations evaluated.

As a mean to control BP, our study has strongly supported the use of combination therapy in hypertensive patients. Our study informs the need to control BP with two or more drugs in most hypertensive patients and on the positive effect on clinical outcomes using combination therapy. Even with the assumption that all drug classes promote similar BP reductions clinically relevant difference exist among specific drugs. Patients initiating with monotherapy ‘never catch up’ with patients initiating on combination therapy as combined therapy will have a major impact on hypertension treatment practice.

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