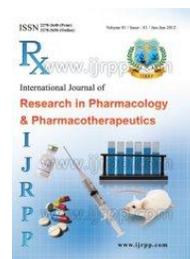




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Research article

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A study on comparison of monotherapy versus combination therapy for hypertensive patients at tertiary care hospital

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ABSTRACT

Objective: To compare the therapeutic benefit of monotherapy and multiple therapy by assessing clinical outcome (BP measurement), To address and document the various adverse effects observed during monotherapy and multiple therapies for hypertensive patients, To compare the cost of both therapies during the treatment.

Material and Methods: Two groups were included during the period of study, monotherapy and second group who received multiple therapy (dual therapy, triple therapy, quadruple therapy); Comparative study was done by measuring the outcome clinically by observing change in the BP. safety of the treatment regimen was assessed by observing the ADRs and cost comparison was carried out between the groups. ANOVA test was applied to check the statistical significance of the above mentioned parameters.

Results: Out of total 200 patients, most of the patients (127) were females and the remaining (73) were males. Among 200 patients enrolled, 152 patients had hypertension along with other co morbidities and diabetes was the most common co morbid condition which was present in 126 patients. Most of patients were treated with monotherapy (96) which was followed by dual therapy (76). In monotherapy T.Furosemide reduced SBP by 50 mmHg and T.Nifedipine and T.Metoprolol Reduced DBP by 20 mmHg, whereas in dual therapy Inj. furosemide, T.Metoprolol decreased mean SBP by 60 mmHg and DBP by 40 mmHg respectively. Results showed that, triple drug therapy was most effective in reducing mean systolic (41.8-24%) and mean diastolic blood pressure (16.8-16.6%) and reduction of SBP by triple therapy was higher compared to other therapies.

Conclusion: Combination therapy reduces both mean systolic and diastolic blood pressure compared to monotherapy. Triple drug therapy is more effective compared to dual and quadruple therapy. Pedal edema due to amlodipine is the most common ADR in both mono and multiple therapies. Combination therapy is more expensive than monotherapy, however triple therapy was most expensive compared to others.

Keywords: Hypertension, Blood pressure, Antihypertensive, Monotherapy, Multiple therapies.

INTRODUCTION

Hypertension is the common disease that is simply defined as the persistently elevated blood pressure of $\geq 140/90$ mm Hg. It characterizes the disease as a progressive cardiovascular syndrome with many causes that result in both functional and structural changes in the heart and vascular system. Hypertension remains one of the most important preventable contributors to disease and death. The risk of cardiovascular (CV) morbidity and mortality is directly correlated with the blood pressure (BP); even patients with the pre-hypertension have an increase risk of CV disease.^[1, 2] High blood pressure is the biggest single cause of death Worldwide through heart attack, stroke and kidney diseases. The situation is graver in world with modernization, we are trading healthy traditional diets for fatty foods, physical jobs for desk bound ones and calm rural life for stressful city life.^[3] Hypertension is a triple paradox: easy to diagnose but often remains undetected, simple to treat but often remains untreated: despite availability of drugs, treatment is not adequately effective.^[4] Significantly, in the majority of cases, a specific underlying cause of hypertension is not known and such patients are said to have essential hypertension.^[5] In India, cardiovascular diseases (CVDs) are estimated to be responsible for 1.5 million deaths annually.^[6] Indeed, it is estimated that by 2020, CVDs will be the largest cause of mortality and morbidity in India.^[7] Hypertension is a major risk factor for CVDs, including stroke and myocardial infarction, and its burden is increasing disproportionately in developing countries as they undergo demographic transition.^[8-11] Previous authors have suggested prevalence rates for hypertension in urban India to be 29-45% in men and 25-38% in women.^[12-15] Hypertension is thought to be less common in rural areas, though data is limited and estimates vary widely depending on the methodology used.^[16-19] The non-modifiable risk factors involved in primary hypertension are age, genetic factors, race etc, The modifiable risk factors are Overweight and obesity, salt intake, environment factors, alcohol, presence of other diseases.^[20-22] Initiation of treatment for elevated blood pressure depends upon the degree of overall cardiovascular risk and level of sustained blood pressure increase. JNC — VIII guidelines recommend that people with

hypertension should lose weight, exercise, drink less alcohol, reduce sodium intake and change their diet.^[1] Many pharmacological agents are available for treating HTN like diuretics, ARBs, ACEIs, CCBs, and many others. The choice of agent for initial therapy depends on the patient's condition and other factors like age and co morbidities. Monotherapy is the standard initial treatment for reducing blood pressure, with stepwise increases in dose if the desired decrease in blood pressure is not achieved. Combining drugs from different classes is approximately 5 times more effective in lowering blood pressure than increasing the dose of 1 drug. Combination therapy is the preferred initial strategy in the treatment of high blood pressure.^[23] A meta-analysis published in 2003 showed that halving the dose of most blood pressure-lowering drugs substantially reduced the prevalence of adverse effects but reduced the blood pressure-lowering effect by only approximately 20%,^[24] supporting proposals for the use of low-dose drug combinations as the first-line treatment for the control of blood pressure.^[25] The effectiveness of this approach relies on there being additive effects between the different classes of drugs when used together, such that the combined blood pressure-lowering effect of 2 together is the sum of each alone. Randomized trials of factorial design are required to quantify the effect of giving 2 drugs together, using 4 groups with 1 drug alone, the other drug alone, both drugs together, and placebo. Such trials have been published on each of the 4 most widely used classes of drugs (thiazides, beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, and calcium channel blockers).^[26] Results obtained from Meta analysis and other large studies show that reduction in blood pressure itself lowers the cardiovascular morbidity and mortality. Still the question remains that how far the monotherapy is effective over multiple drug therapy.^[27] Multiple drug therapy is essential in the compelling indications whereas in case of non- compelling indications both mono and multiple therapies can be used.^[1] Considering the statement mentioned above, this study was carried out to ascertain the kind of therapy which need to be implemented to improve the blood pressure control and to reduce cardiovascular risks to the patients.

MATERIALS AND METHODS

Institutional Ethical Committee clearance was obtained before commencement of the study.

Study design

It is a cohort prospective study.

Study duration

The study was conducted for a period of 6months.

Site of study

Data was obtained from prospective series of patients who were admitted to medicine wards of St. Philomena's Hospital, Bangalore.

Study criteria

Inclusion criteria

- All patients who are admitted in the hospital for the treatment of hypertension.
- All primary hypertensive patient with or without co morbidities (DM ,CV , CKD ,IHD ,stroke)

Exclusion criteria

- Patients suffering from secondary hypertension.
- Pregnant and Lactating females.
- Pediatric patients.

Patients were enrolled in the study as per the inclusion criteria after obtaining written informed consent for the same.

Two groups were included during the period of study monotherapy and second group who received multiple therapy(dual therapy, triple therapy, quadruple therapy) ; Comparative study was done by measuring the outcome clinically by observing change in the BP. safety of the treatment regimen was assessed by observing the ADRs and cost comparison was carried out between the groups.

ANOVA test was applied to check the statistical significance of the above mentioned parameters.

RESULTS

Out of 200 patients, most of the patients (127) were females and the remaining (73) were males (figure 1). Among 200 patients enrolled, 152 patients had hypertension along with other co morbidities and diabetes was the most common co morbid condition which was present in 126 patients (Table 1). In our study most of patients were treated with monotherapy (96) which was followed by dual therapy (76) (Table

1). In monotherapy T.Furosemide reduced SBP by 50 mmHg and T.Nifedipine and T.Metoprolol Reduced DBP by 20 mmHg (Table 3), whereas in dual therapy Inj. furosemide, T.Metoprolol decreased mean SBP by 60 mmHg and DBP by 40 mmHg respectively (Table 4). In case of triple therapy combination of T.Amlodipine ,T.Atenolol ,T.Olmesartan reduced mean SBP by 90 mmHg and DBP by 50 mmHg (Table 5) and in quadruple therapy, both combinations used decreased mean systolic BP and mean diastolic BP by 30mmHg and 10mmHg respectively (Table 6). Results showed that, triple drug therapy was most effective in reducing mean systolic (41.8-24%) and mean diastolic blood pressure (16.8-16.6%) and reduction of SBP by triple therapy was higher compared to other therapies (Table 7). We observed that the most expensive treatment option in terms of per day cost was triple drug therapy (17.14 Rs /day) (Table 8). we carried out ANOVA test to determine statistical significant difference of systolic and diastolic blood pressure reduction between monotherapy and combination antihypertensive therapy to compare the effectiveness of monotherapy with other combination therapies. We observed that maximum systolic and diastolic blood pressure reduction was achieved with triple drug therapy compared to mono, dual and quadruple therapy (Table 9). However, only systolic blood pressure reduction by triple therapy was found to be statistically significant, ($p < 0.019$) but diastolic blood pressure reduction was not found to be statistically significant (Table 10). In our study we found total 23 ADRs, the most common ADR observed was pedal edema by Amlodipine in 10 patients followed by tachycardia with Telmisartan (Table 11).

DISCUSSION

A prospective cohort study was taken up to ascertain the kind of therapy that has to be implemented to improve the BP control for period of six months at St. Philomena's Hospital, Bangalore. During the study period, all patients suffering from hypertension who were admitted to the medicine ward were included in the study. Patients with secondary hypertension, pregnancy and below 18 years were excluded. Institutional Ethical Committee clearance was obtained before commencement of the study. A total number of 200 patients fulfilling the inclusion criteria

were recruited for the present study, and data was obtained from prospective series of patients who were admitted to medicine wards. Out of 200 patients enrolled, age group of patients ranged from 24 to 93 years. In our study majority of patients (71) were in the age group of 74-83 years followed by 64-73 years (41 patients). Data from the various epidemiological studies shows that incidence of hypertension is much higher in elderly population.^[8-11] The results reveal that from 200 patients enrolled, 127 (63.5%) were female and 73 (36.5%) were male whereas study carried out by Nazeer et al, 2010 showed that out of 180 patients recruited in their study 106 (59%) of the patients were males and 74 (41%) patients were females. Previous epidemiological studies have suggested prevalence rates for hypertension in urban India to be 29-45% in men and 25-38% in women.^[14-17] Family history of hypertension of the patients recruited in the present study showed that in majority of patients (140-70%) family history of HTN was unknown and it was present in 19 (9.5%) patients. The results reveal that from 200 patients enrolled, 105 patients (52.5%) are housewives, 62 patients (31%) are retired and 33 patients (16.5%) are working. Occupation of patients recruited in the present study showed that no relation between occupation and occurrence of hypertension. In 48 patients (24%) hypertension was present without any comorbidity. In 152 patients (76%) hypertension was present along with other comorbidities and DM was found to be the most common comorbid condition (63%) followed by IHD (28.5%). The similar results were reported by Prasad Y et al, 2011 where majority of patients were admitted with hypertension and diabetes (112) out of 576 patients. Total of 96 patients (48%) received monotherapy which was followed by dual therapy in 76 (38%) and triple therapy in 21 (10.5%) of patients. Our findings were similar with the study carried out by E. Etuk et al, 2008 and H. Tiwari, 2004 where 48% and 58.6% of patients received monotherapy for blood pressure reduction respectively. However our results were not similar with study carried out by Brent M. et al, 2012 where 91% of patients received combination therapy. In monotherapy, amlodipine was the most commonly prescribed drug in 31 patients (32.29%) followed by Telmisartan in 22 (22.91%) of the patients, but our data was not consistent with the data of Lee Ky Van,

2006 and E. Etuk, 2008 where majority of the patients (32%) received ARBs and Diuretics (44.8%) respectively. In our study, drugs belonging to the class of diuretics and ARBs (17 patients) were the most commonly prescribed as dual therapy and drugs belonging to the class of ARBs, diuretics and CCBs were the most commonly prescribed as triple therapy (8 patients). Out of 200, 7 patients received quadruple therapy, details regarding which are given in the table no.8. Our results showed that, triple drug therapy was most effective in reducing mean systolic BP (41.8-24%) and mean diastolic blood pressure (16.8-16.6%) compared to other therapies. Similar results were reported by David A et al, 2009, where they demonstrated more pronounce BP lowering effects with triple drug therapy compared to dual component therapy, however our results are not consistent with the study carried out by Brent M where they concluded that greater use of single-pill combinations as initial therapy may improve hypertension control and cardiovascular outcomes. In our study 27 patients in Dual therapies, 17 patients in Triple therapies and 3 patients in Quadruple therapies use Fixed Dose Combination. Whereas 49 patients in Dual therapies, 4 patients in Triple therapies and 4 patients in Quadruple therapies use individual therapy. We carried out ANOVA test to find out the significance between the difference in mean BP reduction by different therapies. From our results we observed that maximum systolic and diastolic blood pressure reduction was achieved with triple drug therapy compared to mono, dual and quadruple therapy. However, only systolic blood pressure reduction by triple therapy was found to be statistically significant, ($p < 0.019$) but diastolic blood pressure reduction was not found to be statistically significant. Study carried out by Egan BM et al, 2012 shows that single pill combination provides better HTN control than free combinations which was statistically significant. Our study also aimed at addressing and documenting various adverse effects observed during monotherapy and multiple therapies for hypertensive patients. We found total 23 ADRs, the most common ADR observed was pedal edema in 10 patients followed by Tachycardia with Telmisartan. We assessed severity of reported ADRs by Hartwig's Severity Assessment Scale and we found that 17 ADRs had severity level of 1 whereas 4

ADRs had the severity level of 3 and rest 2 ADRs had the severity level of 2. The details regarding the same are given in Table no. 19. We also compared the cost of mono and multiple therapy. We found that the most expensive treatment option in terms of per day cost was triple drug therapy (17.14 Rs /day) followed by quadruple therapy (12.89Rs/day) other

cost details are given in the Table no.18. Based on the results of our study and the literature, we would conclude that combination therapies (triple therapy) effectively reduce both systolic and diastolic BP. However, the per day cost of combination therapy (triple therapy) was higher compared to monotherapy.

Table no. 1: Distribution of existing comorbidities present in the patients

Disease	Number of patients	Percentage (%)
Diabetic mellitus	126	63
Ischemic Stroke	3	1.5
Ischemic Heart Disease	57	28.5
Lower Respiratory Tract Infection	13	6.5
Chronic Kidney Disease	24	12
Hypothyroidism	22	11
Asthma	16	8
Parkinson	6	3
Embolism	4	2
Chronic Obstructive PulmonaryDisease	3	1.5
Vit. B12 deficiency	9	4.5
Encephalopathy	4	2
Iron deficiency	3	1.5
Tuberculosis	6	3

Table no. 2: Distribution of patients according to type of antihypertensive therapy prescribed

Therapy	Number of patients	Percentage (%)
Mono Therapy	96	48
Dual Therapy	76	38
Triple Therapy	21	10.5
Quadruple Therapy	7	3.5
Total	200	100

Table no. 3: Details of mean BP reduction by drugs used in monotherapy

Drugs	1 ST Day Mean BP (mmHg)	Last Day Mean BP (mmHg)	Mean Hospital Stay (days)	Systolic Reduction (mmHg)	Diastolic Reduction (mmHg)
T.Telmisartan	147/90	137/81	6	11	8
Inj.Furosemide	155/90	136/87	8	19	3
T.Metoprolol	130/90	100/70	4	30	20
T.Furosemide	180/100	130/90	5	50	10
T.Nifedipine	130/90	110/70	2	20	20
T.Amlodipine	133/86	131/84	4	2	2
T.Losartan	141/76	124/71	6	17	5
T.Atenolol	140/80	120/80	10	20	0
T.Olmesartan	120/80	110/70	10	10	10

Table no. 4: Details of mean BP reduction by drugs used in dual therapy

Drugs	1ST Day Mean BP (mmHg)	Last Day Mean BP (mmHg)	Mean Hospital Stay (days)	Systolic Reduction (mmHg)	Diastolic Reduction (mmHg)
Olmesartan + Hydrochlorothiazide	130/70	120/70	2	10	0
Inj.Furosemide, T.Valsartan	130/80	120/70	10	10	10
T.Losartan, T.Amlodipine	140/90	140/80`	3	0	10
Inj.furosemide, T.Telmisartan	130/80	90/60	3	40	20
T.Furosemide, T.Carvedilol	220/110	180/100	6	40	10
T.Ramipril ,T.amlodipine	160/90	120/80	8	40	10
T.Amlodipine + Atenolol	140/80	120/80	10	20	0
Inj.Furosemide , T.Ramipril	220/110	180/100	3	40	10
Inj.Furosemide , T.metoprolol	180/110	120/70	4	60	40
T.Amlodipine , T.Telmisartan	190/100	170/90	7	20	10
T.Clindipine + Telmisartan	140/70	110/60	8	30	10
T.Metoprolol , T. Ramipril	150/90	140/90	4	10	0
T.Losartan +hydrochlorothiazide	170/100	140/80	4	30	20
T.Spironolacton, T.Furosemide	130/90	120/80	4	10	10
T.Telmisartan + Amlodipine	160/90	140/90	4	20	0
T.Telmisartan + Hydrochlorothiazide	130/80	120/80	10	10	0
T.Olmesartan , inj.Furosemide	170/110	120/80	8	50	30
T.Olmesartan + Hydrochlorothiazide	130/70	120/70	2	10	0
T.Nebivolol , T.Furosemide	160/90	150/90	7	10	0

Table no. 5: Details of mean BP reduction by drugs used in triple therapy

Drugs	1 ST Day Mean BP (mmHg)	Last Day Mean BP (mmHg)	Mean Hospital Stay (days)	Systolic Reduction (mmHg)	Diastolic Reduction (mmHg)
T.Olmesatan + Hydrochlorothiazide, T.Amlodipine	170/90	130/70	6	40	20
T.Nebivolol + Hydrochlorothiazide, Inj.Furosemide	180/100	130/90	5	50	10
T.Amlodipine, T.Nebivolol, T.Ramipril	160/80	130/70	6	30	10
T.Amlodipine , T.Atenolol , T.Olmesartan	240/150	150/100	6	90	50
T.Telmisartan + Hydrochlorothiazide , inj.Furosemide	160/90	120/80	8	40	10
T.Losartan + Hydrochlorothiazide, T.Amlodipine	170/90	140/80	6	30	10

Table no. 6: Details of mean BP reduction by drugs used in quadruple therapy

Drugs	1 ST Day Mean BP (mmHg)	Last Day Mean BP (mmHg)	Mean Hospital Stay (days)	Systolic Reduction (mmHg)	Diastolic Reduction (mmHg)
T.Metoprolol, T.Losartan , T.spironolacton , T.Amlodipine	160/90	130/80	7	30	10
T.Losartan + Hydrochlorothiazide, T.Amlodipine, T.Metoprolol	170/90	140/80	6	30	10

Table no. 7: Comparison of mean BP reduction and percentage reduction by different types of therapies

Therapy	1 ST Day Mean BP (mmHg)	Last Day Mean BP (mmHg)	Systolic Reduction (mmHg)	Diastolic Reduction (mmHg)	Systolic Reduction Percentage*(%)	Diastolic Reduction Percentage** (%)
Mono Therapy	141.8/86.9	122/78.1	19.8	8.8	14	10
Dual Therapy	156/89.5	132/80.5	24	9	15	10
Triple Therapy	172.9/97.1	131.4/81.4	41.8	16.1	24	16.6
Quadruple Therapy	165/90	135/80	30	10	18	11

Table no.8: Cost comparison of different types of therapies

Type of Therapy	Cost per Day
Mono Therapy	3.83
Dual Therapy	10.24
Triple Therapy	17.14
Quadruple Therapy	12.89

Table no. 9: Details of ADRs observed during the study period

Drug	Number of ADR	ADR	management	Severity
T.Amlodipine	8	Pedal edema	No drug given	Mild (level 1)
T.Amlodipine	2	Pedal edema	Inj.Furosemide	Mild (level 2)
T.Telmisartan	9	Tachycardia	No drug given	Mild (level 1)
T.Ramipril	4	Dry cough	Change to ARBs	Moderate (level 3)

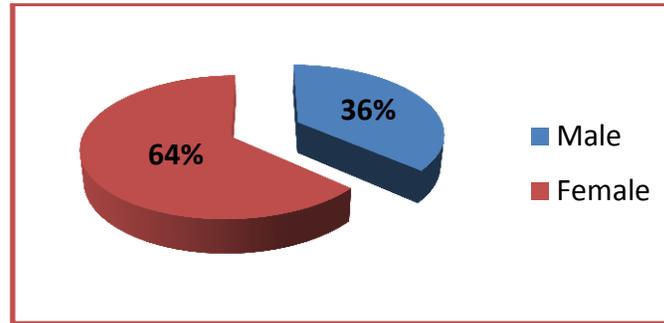
Table no. 10: Comparison of effectiveness of various antihypertensive therapies

Types of therapy		Number of patients	Mean BP reduction	Standard Deviation
Systolic Difference (mmHg)	Mono Therapy	96	19.06	19.793
	Dual Therapy	76	23.55	35.467
	Triple Therapy	21	40.48	36.943
	Quadruple Therapy	7	30.00	.000
	Total	200	23.40	28.977
Diastolic Difference (mmHg)	Mono Therapy	96	8.17	18.492
	Dual Therapy	76	7.11	14.680
	Triple Therapy	21	14.76	21.359
	Quadruple Therapy	7	10.00	.000
	Total	200	8.52	17.185

Table no. 11: ANOVA TEST

		Sum of Squares	Df	Mean Square	F	p-value
Systolic Difference (mmHg)	Between Groups	8236.34	3	2745.44	3.387	
	Within Groups	158851.65	196	810.46		
	Total	167088.000	199			0.019
Diastolic Difference (mmHg)	Between Groups	997.619	3	332.54	1.128	
	Within Groups	57772.301	196	294.75		
	Total	58769.920	199			0.339

Figure no. 1: Division of patients based on their Gender



CONCLUSION

Combination therapy reduces both mean systolic and diastolic blood pressure compared to monotherapy. Triple drug therapy is more effective compared to

dual and quadruple therapy. Pedal edema due to amlodipine is the most common ADR in both mono and multiple therapies. Combination therapy is more expensive than monotherapy, however triple therapy was most expensive compared to others.

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