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A comparative study of monotherapy versus combination therapy in patients with stage-1 hypertension in terms of efficacy and cost effectiveness and to assess the medication adherence

Ritu A Mathew[1], Samuel Johnson[1], Shalumol Jose[1], Shampa Chakraborty[1], Kenneth N*[1], Veeranna Gowda[2]

[1]Department of Pharmacy Practice, The Oxford College of Pharmacy, Begur Road, Hongasandra, Bangalore - 560068, Karnataka, India
[2]Department of General Medicine, The Oxford Medical College, Hospital & Research Centre, Yadavanahalli, Attibele Hobli, Anekal Taluk, Bangalore – 562107, Karnataka, India

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ABSTRACT

Hypertension has multiple pathogenesis and majority of patients require two or more antihypertensive drugs to provide optimum control of blood pressure. The aim is to compare the effectiveness of mono therapy versus combination therapy in patients with stage-1 hypertension, to assess the medication adherence and to compare the cost incurred per day for the different therapies. Patient's demographical details and history was recorded in a data entry form. Outcome of the treatment was measured in terms of reduction in systolic and diastolic blood pressure. Patient's medication adherence was assessed using modified Medication Adherence Scale. Economic outcomes were measured in terms of cost of individual therapy. The data was entered into the excel sheet and statistically analysed using ANOVA. Results showed that dual therapy is the most effective in reducing the mean systolic (28.75 mm Hg) and diastolic (8.875) blood pressure with the combination of Amlodipine + Telmisartan being the most effective. Here, 66 patients (33%) were found to be adherent and 134 patients (67%) were found to be non- adherent. It was found that AMLOKIND 2.5, LOSAKIND and ATEN 50 were the most cost effective brands of drug from the classes of calcium channel blockers, angiotensin receptor blockers and beta blockers respectively. Comparison of effectiveness of various antihypertensive therapies showed that dual therapy shows maximum reduction in mean systolic BP and thus it can be prescribed more often in Stage I hypertensive patients. The poor adherence scores indicate that a multidisciplinary approach with a greater involvement of the patient is required to increase the compliance of the patient. Also cost effective drugs need to be prescribed more in order to decrease the financial burden on the patients.

* Corresponding Author

Name: Dr. Kenneth N
Phone: +91-9944944116
Email: kenneth25in2004@gmail.com

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INTRODUCTION

Hypertension is the third most important risk factor which adds on to the attributable burden of disease in South Asia (Lim SS *et al.*, 2010). According to the data published by the World Health Organization (WHO), the most important cause of premature deaths worldwide is hypertension (Mackay J *et al.*, 2004). As per the WHO 2008 estimates, the prevalence of hypertension in India was found to be 32.5% with

the prevalence rate in men being 33.2% and that in women being 31.7% (Alwan A *et al*., 2011). However, the results from a multicentre study in India on awareness, treatment, and the adequacy of control of hypertension (HTN) showed that only 25.6% of hypertensives undergoing treatment were successful in keeping their blood pressure under control. (Hypertension Study Group, 2001).

The choice of initial therapy varies, depending upon the patient's conditions, age and co-morbidities. Usually monotherapy is considered as a standard initial treatment for hypertension and the dose is gradually increased when the desired goal of the treatment is not achieved (Azad S *et al*., 2015). Since hypertension has multiple pathogenesis, therefore the majority of patients require two or more antihypertensive drugs which act through different mechanisms to provide optimum control of blood pressure (Balraj MS *et al*., 2015). Co-administration of two or more selected anti-hypertensives is considered as the rational combination therapy. Blood pressure (BP) elevations are usually multifactorial, so it makes it very difficult to identify a specific cause for hypertension. Due to different pathophysiologic mechanisms, drug therapy acting on one component produces counter regulatory responses which reduces the effect of that particular agent. As a result the only limited reduction of BP is seen. Most of the antihypertensive agents produce dose dependent side effects such as high dose monotherapy leads to adverse events. Here, in order to minimize dose dependent side effects, lower dose of the initial agent in combination with other antihypertensive is preferred (Gradman A *et al*., 2015).

Excessive reduction in BP, increased incidence of side effects and difficulty in determining the drug responsible for a particular side effect, are a few of the disadvantages associated with the use of combination therapy as the initial treatment for hypertension (MacDonald T *et al.*, 2015).

Adherence

Hypertensive patients need to be prepared for antihypertensive treatment for a lifelong period. Factors that lead to less effective treatment are imperfect execution of dosing regimen and discontinuation of the treatment. Execution of the dosing regimen can be expressed by the term, adherence or compliance (Urquhart J, 1997). Adherence is defined by WHO as ''the extent to which a person's behavior–taking medication, following a diet, and/or executing lifestyle changes-corresponds with agreed recommendations from a health care provider'' (Sabate E, 2003). According to the studies conducted worldwide, it is seen that half of the patients suffering from high BP do not take any treatment even after the availability of effective medical treatment (ME Inkster *et al.*, 2006). Around 50-70% of people do not take their antihypertensive medications as directed by the physician and this is the most important cause that contributes to uncontrolled blood pressure as described by WHO (Mant J *et al*., 2006).

In a study, the adherence was assessed by using Modified Medication Adherence Rating Scale (MMARS). Scores were given based on the patient's response to the questions in the scale. Each response carried a score: none of the time=4, some of the time= 3, most of the time= 2 and all the time= 1. The total scores were added for each patient and can range from 7 to 28. Lower scores would reflect poorer adherence to medication therapy. A full score of 28 or a score of 27 were defined as adherence. A score of 26 and below was categorised as non- adherence (Paraidathathu T *et al.*, 2012).

Cost

Hypertension needs long-term treatment as it is one of the major causes of morbidity and mortality. For the practice of medicines in the developing countries, pharmacoeconomics plays an important role. Compliance with treatment and rational drug prescription is mainly influenced by the cost of the drugs which is an important factor. There is a large difference in the selling price of many branded formulation of the same drug manufactured by the pharmaceutical industries. Clinicians mostly prescribe drugs by brand names in India which adversely affect the patient's finance when a costly brand is prescribed in diseases like hypertension which require long duration of treatment. There is not much awareness among Indian doctors regarding different brands of the same drug. If information about drug prices was readily available, then physicians could provide better services and reduce the cost of drugs by opting for a cost effective treatment. This would be especially beneficial for patients having a poor economic background (Kamath L *et al*., 2016). Very few studies have been carried out with regards to comparison of the different therapies used in hypertension based on their effectiveness in reducing the systolic and diastolic blood pressure. The results of our study would thus help in providing some helpful insights in this field.

MATERIALS AND METHODS

It was a prospective observational study approved (Ref no: IEC/TOMCHRC/049/15-16) by the Institutional Ethics Committee of The Oxford Medical College, Hospital and Research Centre, Attibele, Bangalore. The study was conducted for a

Table 1: Modified medication adherence rating scale

QUESTIONS	SCORES
1. How often do you forget to take your medicine?	
2. How often do you decide not to take your medicine?	
3. How often do you miss taking you medicine because you feel better?	
4. How often do you decide to take less of your medicine?	
5. How often do you stop taking your medicine because you feel sick due to effects of the medicine?	
6. How often do you forget to bring along your medicine when you travel away from home?	
7. How often do you not take your medicine because you run out of them at home?	

Notes: Median score (in quartile range): 27(25-28). Adherence scores scales: 4, none of the time; 3, some of the time; 2, most of the time; 1, all of the time

period of six months. A total of 200 patients of both gender, aged above 18 years, who were given informed consent, suffering from stage-1 hypertension with or without co-morbidities from both the in-patient and out-patient of the General Medicine department were included for this study. The sources of data included patient case records, out-patient card and interview with patients. Patients' not willing to give informed consent, aged below18 years, pregnant women and patients suffering from secondary hypertension were excluded from the study. Along with other details like duration, severity of hypertension and BP measurements of in-patients were documented on a daily basis and BP of out-patients were documented when they came for subsequent follow ups (1st and 2nd follow up).

Outcome of the treatment was measured in terms of reduction in systolic and diastolic blood pressure. The medication adherence was assessed by using Modified Medication Adherence Rating Scale (MMARS) (Paraidathu T *et al.*, 2012) which is shown in table 1. Economic outcomes were measured by comparing the cost of different brands of the same class of drug.

Comparative study was done by measuring the outcome clinically by observing the change in the blood pressure. ANOVA test was performed to check the statistical significance of the above mentioned parameters using Microsoft Excel 2013.

RESULTS AND DISCUSSION

A total of 200 patients who fulfilled the inclusion criteria were included in the study whose ages ranged from 29 to 85 years. The majority of patients (57- 28.5%) were from the age group of 60-69 (Figure 1). Out of the 200 patients enrolled 119 (59.5%) were females and 81 (40.5%) were males (Figure 2). A total of 100 (50%) patients received monotherapy, followed by dual therapy in 82 (41%) and triple therapy in 18(9%) patients (Figure 3). In monotherapy, Telmisartan was found to be the most effective in reducing the systolic and the diastolic BP by a factor of 20 and 14 respectively (Table 2). In dual therapy, the combination of Amlodipine + Telmisartan reduced the SBP by 36mm Hg and the diastolic BP by 15 mmHg (Table 3). In triple therapy, a combination of Amlodipine + Atenolol + Losartan, Amlodipine + Atenolol + Telmisartan and Spironolactone + Propranolol + Furosemide were found to decrease the SBP by 20 mm Hg. Also Amlodipine + Atenolol + Losartan and Amlodipine + Hydrochlorothiazide + Losartan were found to decrease the DBP by 11 mm Hg. (Table 4).

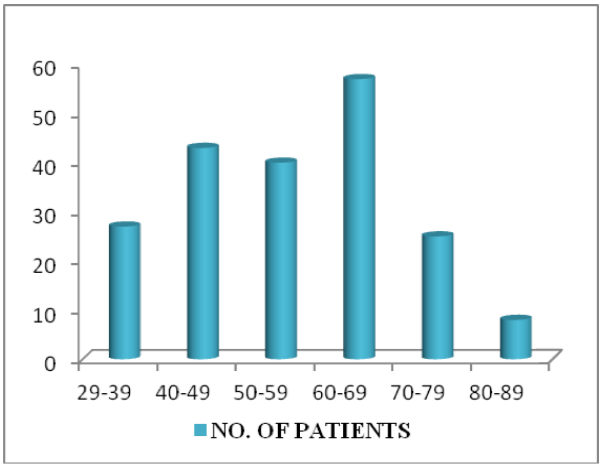

Figure 1: Age wise distribution

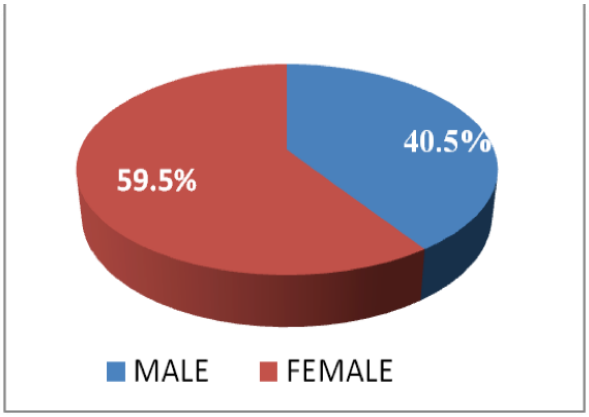

Figure 2: Gender wise distribution

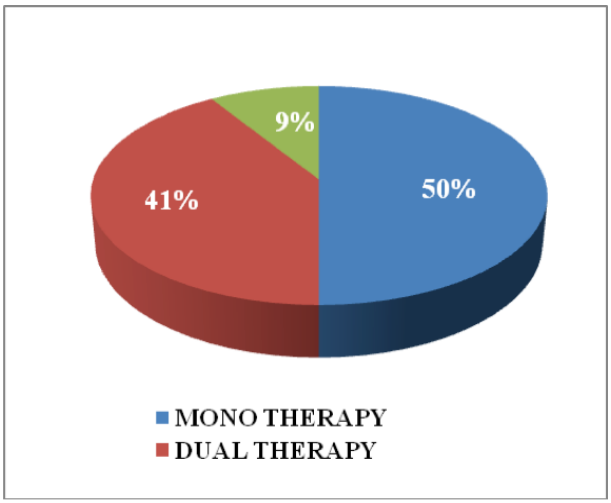

Figure 3: Therapy wise distribution of patients

Results were indicated that a combination of two drugs was the most effective in reducing the mean systolic (28.75-19.70%) and mean diastolic (8.875-7.57%) blood pressure (Table 5). Our study results contradict with other studies (Calhoun *et al.*, 2009 and Azad S *et al.*, 2015) where a more pronounced BP lowering effect was seen with triple therapy as compared to dual therapy. ANOVA test was carried out to determine whether the difference in mean systolic and diastolic reduction by different therapies was significant. The systolic BP reduction was found to be significant ($p < 0.05$) but the diastolic BP reduction was found to be insignificant (Table 6). Similar results were obtained from the study conducted by Azad and co-workers (Azad S *et al.*, 2015).

Table 2: Details of mean BP by various drugs used in monotherapy

S. No	Drugs	1st Day Mean BP/2nd Follow Up BP	Last Day Mean BP/ 2nd Follow Up BP	Systolic Reduction	Diastolic Reduction
1.	Amlodipine	145/88	131/81	14	7
2.	Telmisartan	143/96	123/82	20	14
3.	Losartan	143/87	129/82	14	5
4.	Propranolol	142/87	136/81	6	6
5.	Atenolol	143/87	132/78	11	9

Table 3: Details of mean BP reduction by various drugs used in dual therapy

S. No	Drugs	1st Day Mean BP/2nd Follow Up BP	Last Day Mean BP/ 2nd Follow Up BP	Systolic Reduction	Diastolic Reduction
1.	Amlodipine + Telmisartan	151/91	115/76	36	15
2.	Amlodipine + Atenolol	146/85	133/80	13	5
3.	Amlodipine + Losartan	147/87	133/80	14	7
4.	Amlodipine + Furosemide	145/85	130/80	15	5
5.	Telmisartan + Furosemide	144/88	134/80	10	8

Table 4: Details of mean BP reduction by various drugs used in triple therapy

S. No	Drugs	1st Day Mean BP/2nd Follow Up BP	Last Day Mean BP/ 2nd Follow Up BP	Systolic Reduc-tion	Diastolic Reduc-tion
1.	Amlodipine + Atenolol + Losartan	154/94	134/83	20	11
2.	Amlodipine + Atenolol + Furosemide	155/85	145/85	10	0
3.	Amlodipine + Atenolol + Telmisartan	153/90	133/83	20	7
4.	Amlodipine+ Hydrochlorothiazide + Losartan	152/93	138/82	14	11
5.	Losartan + Hydrochlorothiazide + Furosemide	153/91	141/84	12	7

Table 5: Comparison of mean BP reduction by different types of therapies

Type of Therapy	1st Day Mean BP	Last Day Mean BP	Systolic Reduction	Diastolic Reduction	Systolic Reduction Percentage	Diastolic Reduction Percentage
Mono Therapy	143.8/89	130.2/80.8	13.6	8.2	9.45%	6.29%
Dual Therapy	145.9/87.4	117.1/78.5	28.75	8.875	19.70%	7.57%
Triple Therapy	153.5/90.7	137.5/83	16	7.67	10.42%	5.57%

Table 6: Details of systolic and diastolic difference by ANOVA test

		Sum of Squares	Degree of freedom	Mean Square	F Value	P Value
Systolic Difference (mm Hg)	Between Groups	3909.472	2	1954.736		
	Within Groups	15767.122	197	80.04	24.423	0.04
	Total	19676.595	199			
Diastolic Difference (mm Hg)	Between Groups	301.559	2	150.779		
	Within Groups	6708.316	197	34.052	4.4278	0.20195
	Total	7009.875	199			

Table 7: Details of adherence scores by patients

Adherence score	Adherence status	Frequency (N)	Percentage (%)
Full Score (28)	Adherers	31	16.5%
27(one point deducted from either question 1 or 6)	Adherers	35	17.5%
27(one point deducted due to other question)	Non Adherers	53	26.50%
23 TO 26	Non Adherers	60	30%
19 TO 22	Non Adherers	12	6%
7 TO 18	Non Adherers	9	4.50%

Adherence

The medication adherence of the patients was assessed by asking them the questions of the modified Medication Adherence Rating Scale. This was a self-reporting questionnaire and one of the disadvantages of using it is that it overestimates adherence as patients tend to give socially acceptable responses that often do not match with their medication taking behaviour. Scores were given based on their answers. Each response carried a score: none of the time=4, some of the time= 3, most of the time= 2 and all the time= 1. The total scores were added for each patient and can range from 7 to 28. Lower scores would reflect poorer adherence to medication therapy. A full score of 28 or a score of 27 were defined as adherence. A score of 26 and below was categorised as non- adherence.

In our study, 66% of the patients were non-adherers and only 34% of the patients were adherers (Table 7). A study was conducted by Fernandez-Arias among hypertensive patients in Lima, Peru with the purpose of evaluating the medication adherence in hypertensive patients.

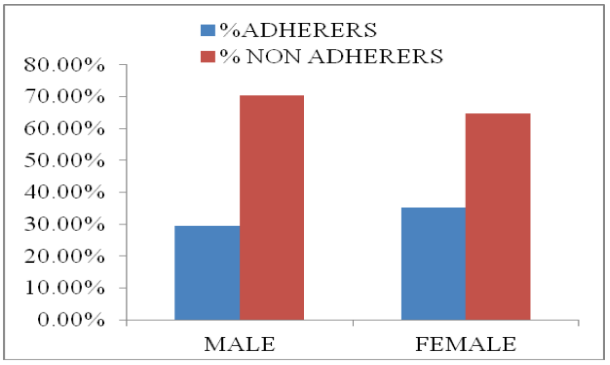

Figure 4: Medication adherence based on gender

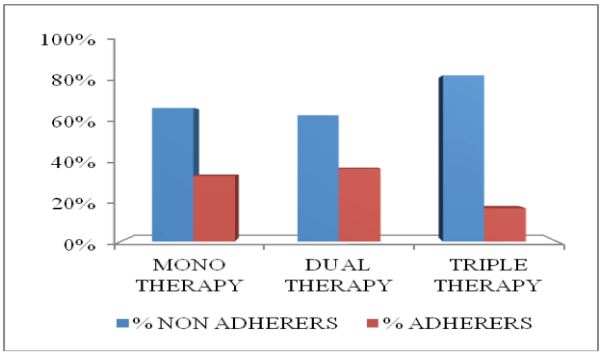

Figure 5: Medication adherence based on therapy

Table 8: Cost per day for various brands of Calcium channel blockers

Brand name	Generic name	Dose	No.of tablets/ day	Cost of one tablet	Cost per day
AMLONG 2.5	AMLODIPINE	2.5	2	1.606	3.212
AMLONG 10	AMLODIPINE	10	1	4.94	4.94
AMLIP 5	AMLODIPINE	5	1	3.18	3.18
AMLIP 2.5	AMLODIPINE	2.5	2	1.98	3.96
AMLOKIND 2.5	AMLODIPINE	2.5	2	0.82	1.64

Table 9: Cost per day for various brands of Angiotensin Receptor Blockers

Brand name	Generic name	Dose	No.of tablet per day	Cost of one tablet	Cost per day
TELMA 20	TELMISARTAN	20	2	3.54	7.08
TELMA 40	TELMISARTAN	40	1	6.42	6.42
TELMIKIND	TELMISARTAN	40	1	3.02	3.02
TELPIC	TELMISARTAN	40	1	8.61	8.61
GOSART	LOSARTAN	50	1	5.2	5.2
LARTAN	LOSARTAN	50	1	3.7	3.7
LOSAR	LOSARTAN	25	2	3.15	6.3
LOSAKIND	LOSARTAN	50	1	2.92	2.92

Table 10: Cost per day for various brands of Beta blockers

Brand name	Generic name	Dose (in mg)	No.of tablets Per day	Cost of one Tablet (in rs.)	Cost per Day (in rs.)
ATEN 25	ATENOLOL	25	2	2.15	4.3
ATEN 50	ATENOLOL	50	1	1.74	1.74
ATEN 100	ATENOLOL	100	1	3.4	3.4
ATENEX	ATENOLOL	50	1	2.35	2.35

The results were found to be similar with 57.4 % of the patients showing low adherence.

In our study, females showed a greater adherence (35.29%) than males (Figure 4) which is similar to the results obtained from other studies (Paraidathu T *et al.*, 2012) where as 56.3% of the females were adherers. Dual therapy was associated with maximum adherence and triple therapy was associated with least adherence (Figure 5).

Cost analysis

Cost minimization analysis was carried out for three classes of drugs including, calcium channel blockers, angiotensin receptor blockers and beta blockers which were commonly prescribed at the study site. Cost minimization analysis is a method of calculating the costs of drug so as to determine the least costly drug. The results revealed that AMLOKIND 2.5 was the cost effective drug in the class of CCBs, with a cost per day of Rs 2.92 (Table 8). LOSAKIND was the most cost effective drug in the class of ARBs (Table 9) and ATEN 50 (Rs 1.74) was the most cost effective drug in the class of beta blockers (Table 10). A single drug is sold under different brand names by various companies and the cost variation between these brands is huge. A costly brand of a particular drug has been scientifically proved to be in no manner better than its cheaper counterpart. Hence prescribing these drugs of cheaper brands will help reduce the economic burden on the patient and will especially be beneficial to the patients belonging from a poor economic background.

CONCLUSION

Comparison of mean BP reduction by different types of therapies showed that dual therapy is the most effective in reducing the mean systolic (28.75-19.70%) and diastolic (8.875-7.57%) blood pressure. As dual therapy has shown greater efficacy in reducing systolic BP it can be prescribed more often in hypertensive patients.

Adherence scores of the patients revealed that out of 200 patients, 66 patients (33%) were found to be adherent and 134 patients (67%) were found to be non- adherent. The adherence scores indicate that a multidisciplinary approach with a greater involvement of the patient is required to increase the compliance of the patient. The patients need to be counselled about the importance of sticking to the prescribed therapy especially in a chronic disease like hypertension.

It was found that AMLOKIND 2.5, LOSAKIND and ATEN 50 were the most cost effective brands of drug from the classes of CCBs, ARBs and beta blockers respectively. The results of our study shown that increased knowledge of the prescriber regarding the various brands and their prices and thus by choosing a cost effective drug reduce the economic burden on the patient.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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