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Research Article

EFFICACY, SAFETY AND COST-EFFECTIVENESS OF FIXED DOSE COMBINATION THERAPY IN MANAGEMENT OF HYPERTENSION

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A B S T R A C T

Background: - Raised blood pressure is one of the major public health challenge and cardiovascular risk factor worldwide. Studies have clearly demonstrated that in 2000, nearly 972 million people in the world suffered from hypertension and it is presumed to increase to 1.56 billion by 2025. In usual practice, treatment of mild to moderate hypertension starts with single drug, though ESH-ESC guidelines recommends initiating treatment with two drugs when blood pressure is >20 mmHg above systolic targets or >10 mmHg above diastolic targets.

Material and Methods: - The study was prospective, open labeled, three armed and randomized. A total of 96 adult hypertensive patients(aged 18 to 60 years) having uncontrolled blood pressure (systolic BP ≥ 140 to 179 mmHg and/or Diastolic BP ≥ 90 to 109 mmHg) on low dose mono-therapy with either Amlodipine (5mg) or Telmisartan (40 mg) were enrolled in the study after obtaining written informed consent. In order to conduct the study approval from the Institutional Ethics Committee was obtained.

Result:- 90.32% patients from combination therapy arm (group C) achieved the target BP, unlike 59.37% cases from group B (treated by amlodipine 10 mg) and 76.66% from group A (treated by Telmisartan 80 mg) had shown this response. 40.63% patients from group B remained hypertensive even after completion of 8 weeks therapy. In our study, maximum ADRs were reported in Amlodipine monotherapy group, though the difference with other treatment groups was not significant. In term of achieving target BP, group B treatment was least effective but had minimum cost of therapy, while group A treatment was more effective than group B but had highest cost of therapy. Group C was on top in achieving target BP and cost of therapy was lower than group A, but higher than group B.

Conclusion:-In this study, fixed dose combination (Telmisartan–Amlodipine) therapy has demonstrated significantly greater BP reductions in terms of Efficacy, safety and Cost-effectiveness for both SBP and DBP compared to mono-therapy in the overall study population.

INTRODUCTION

Raised blood pressure is one of the major public health challenge and cardiovascular risk factor worldwide. Studies have clearly demonstrated that in 2000, nearly 972 million people in the world suffered from hypertension and it is presumed to increase to 1.56 billion by 2025.[1] The 7th report of Joint National Committee in 2003[2] and the European guidelines 2007 and 2009, recommend that the primary step to curb hypertension is lifestyle modification prior to commencement of medical treatment which includes losing weight, exercising, changing diet[3]. Several programs that are aimed to reduce psychological stress such as biofeedback; relaxation and meditation also aids in reducing hypertension.

There are a variety of classes of high blood pressure medications. The aim of the therapy is to reduce blood pressure to <140/90 mmHg for most individuals with Chronic kidney diseases and/or Diabetes unlike individuals with more than 60 years (the target blood pressure is set Higher).[4] When the desired blood pressure goal is not achieved, a change in treatment should be made as therapeutic inertia is a defined hindrance to control blood pressure (Eni C. Okonofua *et al* 2006). Guidelines on the anti-hypertensive therapy and choice of agents for various subgroups have changed over time and it

varies among different countries. There is no consensus over the best first line agent for hypertension. [5] The UK guidelines support calcium channel blockers (CCB) for older people (> 55 years) and angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARB) for younger people (National Institute Clinical Excellence, August 2011).[6] The Cochrane collaboration, World Health Organization and the United States guidelines emphasis on low dose thiazide diuretic as first line treatment.[7] In Japan, following six classes of antihypertensive drugs: CCB, ACEI/ARB, thiazide diuretics, beta-blockers, and alpha-blockers are considered reasonable while in Canada alpha-blockers are recommended as optional.[5]

Most people need more than one drug to control their blood pressure[1,4]. In usual practice, treatment of mild to moderate hypertension starts with single drug, though ESH-ESC guidelines recommends initiating treatment with two drugs when blood pressure is >20 mmHg above systolic targets or >10 mmHg above diastolic targets.[8] In combination drug therapy of hypertension, renin–angiotensin system inhibitors and calcium channel blockers, or renin–angiotensin system inhibitors and diuretics are the most preferred combinations.[9] Other combinations which are justifiable include beta-blockers and diuretics, calcium channel blockers and diuretics, and dihydropyridine calcium channel blockers and beta-blockers. Unjustifiable combinations are beta-blockers and non-dihydropyridine calcium blockers (such as verapamil or diltiazem), beta-blockers and centrally acting agents, and dual renin–angiotensin system blockade (e.g. angiotensin receptor blocker + angiotensin converting enzyme inhibitor). [9]

MATERIAL AND METHODS

The study was prospective, open labeled, three armed and randomized. It was conducted in the Out-Patient Department of tertiary care Hospital of North India. In order to conduct the study Approval from the Institutional Ethics Committee was obtained. A total of 96 adult hypertensive patients(aged 18 to 60 years) having uncontrolled blood pressure (systolic BP ≥ 140 to 179 mmHg and/or Diastolic BP ≥ 90 to 109 mmHg) on low dose mono-therapy with eitherAmlodipine (5mg) or Telmisartan (40 mg) were enrolled in the study after obtaining written informed consent. Patients with other concomitant medical conditions, alcohol or drug dependence, pregnant and lactating women and cases of secondary hypertension were not included in the study.

Each enrolled patient was subjected to detailed medical history, demography and physical examination. Measurements of systolic and diastolic BP were taken manually with a calibrated mercury sphygmomanometer in sitting position. Three measurements of BP were taken (each 5 minutes apart) and average value was noted down. Blood samples were obtained for testing of blood sugar, renal function, liver function and lipid profile.

Patients were randomized in three treatment groups as following:

- **Group A:** In this group, patients were put on high dose mono-therapy of Telmisartan 80 mg, once daily for 8 weeks.
- **Group B:** In this group, patients received high dose mono-therapy of Amlodipine 10 mg, once daily for 8 weeks.
- **Group C:** In this group, patients received fixed dose combination of Telmisartan 40 mg and Amlodipine 5 mg, once daily for 8 weeks.

Patients were regularly follow-up after 2 weeks, 4 weeks and 8 weeks. At each visit, complete clinical examination was carried out, including recording of systolic and diastolic blood pressure (BP). Safety was assessed in terms of both subjective and objective systemic adverse-effects. Subjective symptoms such as headache, dizziness, fatigue, back pain, dyspepsia, myalgia, pruritus and nausea were assessed by interrogating the patient at each visit. Objective signs like rash, edema and hypotension were also obtained.

RESULT AND DISCUSSION

Efficacy

A study conducted in Japan reported that low dose combination of Telmisartan 40 mg and Amlodipine 5 mg significantly reduced 24hr mean and clinical BP in patients whose hypertension was not controlled by 5 mg of Amlodipine.[10] Recently, in ONTAR-GET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial), Telmisartan indicates a non-inferior capacity than ramipril to prevent CV events in high-risk patients.[11] As a consequence of these results,FDA has approved an expanded indication for Telmisartan for reducing the risk of MI, stroke, or death from cardiovascular diseases in patients aged 55 years or older who are intolerant to ACE inhibitors but at high risk for CV events.

Results of a TEAMSTA 5 study also revealed that combination treatment was more efficacious than single drug therapy in reducing SBP and DBP. The PBAC noted the addition of Telmisartan (T) 40 mg to Amlodipine (A) 5 mg produced statistically significantly larger reductions in trough seated diastolic blood pressure (DBP) than Amlodipine 5 mg alone.[12] Clinical evidence and guidelines suggest the use of combination treatments to provide additional antihypertensive efficacy in patients who are not controlled with monotherapy. There are indications that combination treatments may not only result in more patients achieving BP target, but may also result in a more rapid BP-lowering effect.[13] In patients with uncomplicated hypertension (risk group A of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high blood pressure [JNC VIII] guidelines[4], the most important goal to prevent cardiovascular outcomes is to lower down blood pressure to <140/90 mm Hg; the choice of agent may be irrelevant, and lifestyle modification is an important primary step in therapy.

Effectiveness of 8 weeks treatment for both SBP and DBP (DBP ≤ 89 mm of Hg and SBP ≤ 139 mm of Hg) in various treatment groups

Figure 1 illustrates the number of patients who became normotensive (DBP ≤ 89 mm of Hg and SBP ≤ 139 mm of Hg) after 8 weeks of therapy in various treatment groups. 90.32% patients from combination therapy arm (group C) achieved the target BP, unlike 59.37% cases from group B (treated by amlodipine 10 mg) and 76.66% from group A (treated by Telmisartan 80 mg) had shown this response. 40.63% patients from group B remained hypertensive even after completion of 8 weeks therapy.

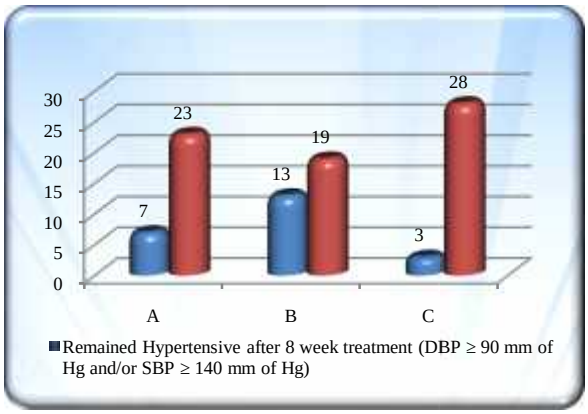

Fig. 1 Graph stating effectiveness of 8 weeks treatment for both SBP and DBP in various treatment groups

Safety

In factorial study, a total of 545 (37.3%) patients reported at least one adverse event during the 8-week study.The most commonly reported adverse events were headache and peripheral edema. In that study, headache was more frequent in the placebo group. The incidence of peripheral edema was highest in the Amlodipine 10 mg group however this rate was lower when Amlodipine was used in combination with Telmisartan.[14]In another study, edema was most commonly reported adverse drug reaction, and was especially seen in Amlodipine group .[15]

In our study, maximum ADRs were reported in Amlodipine monotherapy group, though the difference with other treatment groups was not significant. About 25% patients reported ADRs like ankle edema, constipation, headache and fatigue (TABLE1). All ADRs were of mild nature and did not require discontinuation of therapy.

Table 1 Distribution of ADRs in various treatment groups (N=18)

Various types of ADRs	Group A	Group B	Group C	Grand Total
Fatigue	2	3	2	7
Nausea	1	1	1	3
Headache	1	1	1	3
Constipation	0	2	0	2
Dizziness	1	1	0	2
Ankle Edema	0	1	0	1
Grand Total	**5**	**9**	**4**	**18**

Cost

In addition to efficacy and safety, the cost of therapy has become an increasingly important inescapable factor to consider when selecting drugs to treat patients with mild-to-moderate hypertension. Many antihypertensive drugs are available in our Country but some are not affordable for majority of the population. The need of the hour is that the nation's health economists have to answer this pharmacoeconomic question. The cost of a combination might be higher than one or the other drug, however, cost effectiveness is to be calculated taking into account the adverse reactions, their treatment, loss of working hours and quality of life affected. In a study conducted in Nigeria, CCB was the second most cost-effective option for medium and high risk patients in order to achieve better health outcomes after thiazide diuretic.[16] In our study the cost of 8 weeks antihypertensive drug therapy was INR 600 in group A, INR 257 in group B and INR 448 in group C. Thus, the maximum financial burden of antihypertensive drug treatment was observed in Telmisartan monothearpy treated group while the cost of Amlodipine monotherapy was found to be the minimum. Simultaneous comparison of cost and efficacy of various treatment groups is illustrated in Table 2. In term of achieving target BP, group B treatment was least effective but had minimum cost of therapy, while group A treatment was more effective than group B but had highest cost of therapy. Group C was on top in achieving target BP and cost of therapy was lower than group A, but higher than group B.

Table 2 Comparison of cost-effectiveness in various treatment groups

Treatment Group	% of cases became Normotensive after 8 wk treatment	Mean Cost of Treatment (INR)
Group A	76.66	600\
Group B	59.37	257
Group C	90.32	448

CONCLUSION

Adequate BP control and reduction of CV events are particularly effective with the combination of antihypertensive agents, including an ACE inhibitor or an ARB. Recently, the combination of an ACE inhibitor or ARB plus a CCB appears to be rational and effective. The rationale for combination therapy with agents that block the renin–angiotensin system (RAS) and a calcium channel blocker (CCB) or diuretic is well founded in growing evidence. It is seen that the combination of a RAS suppressor and a dihydropiridinic CCB would offer additional benefits independently of BP reduction. A Telmisartan – Amlodipine combination has demonstrated significantly greater BP reductions compared with each monotherapy component in the overall population, and particularly in patients with moderate to severe hypertension and high-risk patients. This combination is well tolerated with a safety profile similar to placebo and is consistent with the known safety profile of its monotherapy components. These combinations can thus be recommended for priority use.

In term of BP control, Fixed dose combination therapy appears a better therapeutic approach than high-dose monotherapy for hypertensive patients who are inadequately controlled by low-dose monotherapy.

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