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RATIONALITY OF THE FIXED DOSE COMBINATION OF TELMISARTAN AND AMLODIPINE IN MANAGEMENT OF MILD TO MODERATE HYPERTENSION UNRESPONSIVE TO LOW DOSE MONOTHERAPY

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ABSTRACT

Hypertension is a persistent medical condition which is specified by elevated blood pressure (BP) in the arteries. The aim of the therapy is to keep BP below 140/90 mmHg for most individuals, though certain studies recommend lesser target BP for those with diabetes or kidney disease. Monotherapy can effectively control BP in limited number of hypertensive patients and most patients require the combination of at least two drugs to achieve target BP. As BP is outcome of several physiological mechanisms, thus an attempt to block one (like monotherapy) tends to raise compensatory activity of others. Telmisartan is a potent, long-lasting, nonpeptide angiotensin II antagonist that acts on the angiotensin 1 (AT1) receptor subtype. Amlodipine, a third generation dihydropyridine calcium channel blocker (CCB), is illustrated by a higher vascular selectivity and a lesser negative inotropic effect compared to other CCBs. Many studies have reported that combination of Amlodipine and Telmisartan showed a statistically significant reduction in SBP and DBP as compared to Telmisartan monotherapy and in DBP as compared to Amlodipine monotherapy. The number of ADRs also is less in combination. The combination is also found to be more cost-effective. Thus, a combination of Amlodipine and Telmisartan is more rational than either of the monotherapy.

KEYWORDS: Combination treatment, mild to moderate hypertension, telmisartan, Amlodipine.

INTRODUCTION

Hypertension (HT) is one of the major public health challenges worldwide and a leading cause of mortality and morbidity globally. It doubles the risk of cardiovascular diseases including coronary heart disease, congestive heart failure, ischemic and hemorrhagic stroke, renal failure and peripheral arterial disease. Inspite of the availability of various drugs for the treatment of HT, large segments of the hypertensive population are either untreated or inadequately treated. (Harrison 19th ed).

According to the Seventh report of the Joint National Committee in 2003 (Chobanian AV et al 2003) and the European guidelines 2007 (Mancia G et al 2007) and 2009 (Mancia G et al 2009), the first step in hypertension control is lifestyle modification which includes dietary changes, physical exercise and weight loss (Siebenhofer et al 2007) followed by medical management. Several classes of antihypertensive drugs are available for the treatment of hypertension. However, there is no consensus over the best first line agent for hypertension (Klarenbach SW et al 2010). Based on pooling results from clinical trials, meta analyses of the efficacy of different classes of antihypertensive agents suggest essentially equivalent blood pressure lowering effects of the following six major classes of anti hypertensive agents when used as monotherapy: thiazide diuretics, beta blockers, ACEIs, ARBs, calcium antagonists, and alpha-1 blockers. (Harrison 19th ed).

In usual practice, treatment of mild to moderate hypertension is started with single drug.(Mancia G et al 2007). But many people require more than one drug to control their blood pressure (Chobanian AV et al 2003, JNC7). In combination drug therapy, renin–angiotensin system inhibitors and calcium channel blockers, or renin–angiotensin system inhibitors and diuretics are the preferred combinations (Sever PS et al 2011).

Telmisartan belongs to the category of angiotensin receptor blockers (ARBs), while amlodipine belongs to calcium channel blockers (CCBs). Both of these drugs are newer agents of their respective classes and have unique advantages as compared to the older agents. (References to be added). Therefore, this study was conducted to assess the rationality of fixed dose combination of telmisartan and amlodipine in management of mild to moderate

hypertension unresponsive to low dose monotherapy in terms of safety, efficacy and cost of therapy.

MATERIAL AND METHODS

This was a prospective, open label, three armed and randomized study. It was conducted in the Out-Patient Department of Medicine, Mahatma Gandhi Hospital, Jaipur, in association with Department of Pharmacology, Mahatma Gandhi Medical College, Jaipur. Approval from the Institutional Ethics Committee was obtained to conduct the study. A total of 96 adult hypertensive patients, fulfilling the inclusion criteria were enrolled in the study.

Inclusion Criteria

1. Patients with essential hypertension with uncontrolled blood pressure (Systolic BP ≥ 140 to 179 mmHg and/or Diastolic BP ≥ 90 to 109 mmHg) who were already on low dose monotherapy with either Amlodipine (5mg) or Telmisartan (40 mg) once daily for ……..
2. Age 18 to 60 years, either gender.
3. Patients who were willing to participate and sign consent document.
4. Patient willing to comply with the protocol requirements.

Exclusion Criteria

1. Secondary Hypertension
2. Patients with essential hypertension who had well controlled blood pressure with amlodipine 5 mg or telmisartan 40 mg daily as monotherapy or who were on other drugs
3. Clinically evident concomitant disorder such as cardiovascular, renal, hepatic, endocrine, neurological, psychiatric or other complicating diseases or severe co-morbidities.
4. Pregnant or lactating women.
5. Female patients of childbearing potential who do not agree to remain abstinent or use medically acceptable methods of contraception during the study period.
6. Patients with known hypersensitivity to any of the test drug.
7. Patients with alcohol or drug dependence.
8. Patients with stage 3 hypertension (Systolic BP ≥ 180 mmHg and/or Diastolic BP ≥ 110 mmHg)
9. Patients who had any major surgery within 4 weeks of screening.
10. Any other condition that in the opinion of the investigator does not justify the patient's participation in the study.

Each patient was subjected to the detailed medical history, demography and physical examination. Measurements of systolic and diastolic BP were performed manually with a calibrated mercury sphygmomanometer in sitting position. Three measurements of BP were taken (each 5 minutes apart) and average value was noted. Blood samples were obtained for testing of blood sugar, renal function, serum electrolytes, 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 had fixed dose combination of Telmisartan 40 mg and Amlodipine 5 mg, once daily for 8 weeks.

Follow-up visits were performed after 2 weeks, 4 weeks and 8 weeks. At each visit, complete clinical examination was carried out, including a 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 questioning the patient at each visit. Objective signs like rash, oedema and hypotension were also obtained. At the end of study i.e. week 8, blood samples were taken for testing blood sugar, renal function, serum electrolytes, liver function and lipid profile.

RESULTS

A total of 96 patients were enrolled in the study including 53 males and 40 females. Their age and sex distribution is shown in tables 1 and 2.

Table 1: Distribution of cases according to their age in different treatment groups.

Age (in years)	Group A	Group B	Group C	Grand Total
21-30	4 (13.33)	4(12.50)	4(12.90)	12 (12.90)
31-40	11(36.67)	10(31.25)	15(48.39)	36(38.71)
41-50	9(30.00)	14(43.75)	11(35.48)	34(36.56)
51-60	6(20.00)	4(12.50)	1(3.23)	11(11.83)
Grand Total	30(100.00)	32(100.00)	31(100.00)	93(100.00)
Mean $\pm$ SD	42.03$\pm$8.64	43.06$\pm$8.98	39.58$\pm$7.293	41.57$\pm$8.38

Table 2: Distribution of cases according to sex in different treatment groups.

Sex	Group A	Group B	Group C	Grand Total
Male	18 (60.00)	20(62.50)	15(48.39)	53(56.99)
Female	12 (40.00)	12(37.50)	16(51.61)	40(43.01)
Grand Total	30(100.00)	32(100.00)	31(100.00)	93(100.00)

Comparison of efficacy across the three treatment arms

1. Effectiveness of 8 weeks treatment for SBP (target SBP ≤ 139 mm of Hg): Though the highest therapeutic response in term of mean reduction in systolic BP from baseline was observed in group C, but if percentage of cases became normotensive was taken into account then group B showed highest response (90.625%) for systolic BP.

After 8 weeks of treatment, SBP target (≤139 mm of Hg) was achieved in 80% cases of group A, 90.625% cases of group B and 90.323% cases of group C. But the difference was statistically not significant (P value = 0.370). (Table 3, Figure 1).

2. Effectiveness of 8 weeks treatment for DBP (target DBP ≤ 89 mm of Hg): DBP target (≤ 89 mm of Hg) after 8 weeks therapy was attained in 96.667% and 96.774% cases of group A and group C respectively. In group B only 68.75% cases achieved DBP target. The difference was found statistically highly significant (P value < 0.001). (Table 4, Figure 2).

3. Effectiveness of 8 weeks treatment for both SBP and DBP (DBP ≤ 89 mm of Hg and SBP ≤ 139 mm of Hg): 90.32% patients from combination therapy arm (group C) achieved the target BP, while only 59.37% and 76.66% cases from group B and group A respectively had shown this response. (Table 5, figure 3)

Table 5: Distribution of cases according to effectiveness of 8 week treatment for both SBP and DBP in various treatment groups.

Status of SBP and DBP after 8 week treatment	Group A	Group B	Group C	Grand Total
Remained Hypertensive after 8 week treatment (DBP ≥ 90 mm of Hg and/or SBP ≥ 140 mm of Hg)	7 (23.34)	13 (40.63)	3 (9.68)	23 (24.74)
Became Normotensive after 8 week treatment (DBP ≤ 89 mm of Hg and SBP ≤ 139 mm of Hg)	23 (76.66)	19 (59.37)	28 (90.32)	70 (75.26)
Grand Total	30 (100.00)	32 (100.00)	31 (100.00)	93 (100.00)

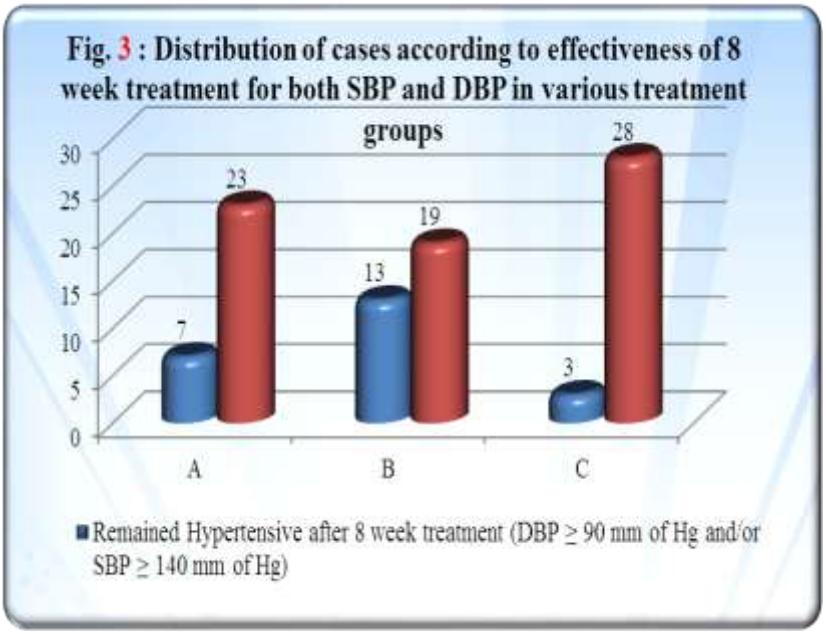

Table 6: shows various adverse drug reactions (ADR) noted in the three treatment groups.

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**

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

Group B showed the maximum no. of adverse effects, (p value????).

We further evaluated the three treatment groups according to the cost of therapy. 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. (Table 24, Figure 22).

Simultaneous comparison of cost and efficacy of various treatment groups is illustrated in Table 25 and Figure 23. 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.

DISCUSSION

Many patients with hypertension require more than one drug for optimum control of blood pressure. When initial monotherapy with an antihypertensive agent does not have the desired BP-lowering effect, either the dose is increased or another antihypertensive drug is added. Often, combinations of agents, with complementary antihypertensive mechanisms are required to achieve goal blood pressure reductions. In combination therapy, the preferred combinations include ARB/ACE –I with CCB or diuretics. (Sever PS et al 2011).

In this study, we tried to compare combination therapy of telmisartan 40 mg with amlodipine 5 mg once daily versus high dose monotherapy (telmisartan 80 mg daily and amlodipine 5 mg daily as individual drug). We noted that combination therapy was most effective in terms of achieving the target blood pressure in maximum number of cases. This is in accordance with a previous study in Japan which reported low dose combination of Telmisartan 40 mg and Amlodipine 5 mg to significantly reduce 24hr mean and clinical BP in patients whose hypertension was not controlled by 5 mg of Amlodipine alone (Ohishi et al 2013). 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 (Neldam et al 2011). Further, it is suggested that combination treatments may not only result in more patients achieving BP target, but may also result in a more rapid BP-lowering effect (Dahlof et al 2005).

Besides efficacy we also evaluated the safety of this combination over high-dose monotherapy. Only 4 patients on combination therapy complained of adverse effects. None of the patients developed oedema. In previous studies, the most commonly reported adverse events were headache and peripheral edema. Headache, however, 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 (Littlejohn et al 2008). In another study, edema was most commonly reported adverse drug reaction, and was especially seen in Amlodipine group (Neldam et al 2010).

Adding a blocker of the renin-angiotensin system (RAS) to a CCB appears to be associated with a reduction in the incidence of CCB-related oedema (Fogari et al 2007). The exact mechanism remains to be established but appears to involve the ability of RAS blockers to

counteract the microcirculatory changes induced by CCBs and dilate venous capacitance vessels (kohlmann et al 2006). Thus, addition of telmisartan provides an additional benefit to patients who develop oedema with amlodipine.

In addition to efficacy and safety, the cost of therapy is an extremely important factor while selecting drugs to treat patients with mild-to-moderate hypertension. Many drugs are available for control of hypertension but many of them may not be affordable for a large section of population. This serious pharmacoeconomic question has to be answered by the nation's health economists. 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 (Ekwunife et al 2013). In our study, the cost of combination was higher than that of amlodipine monotherapy, but the clinical outcome was better in terms of achieving target BP and adverse events.

Rationale of combination of Telmisartan and Amlodipine

When initial monotherapy with an antihypertensive agent does not have the desired BP-lowering effect, either the dose of the drug is increased or another drug from another class of antihypertensives is added. Uptitrating amlodipine from 5 mg to 10 mg may improve BP response rates but typically also increases the incidence of side effects especially edema, which, in turn, may lead to reduced patient compliance and possibly to treatment discontinuation. To achieve the specified BP goals and to reduce the risk of CV morbidity and mortality, the majority of patients with hypertension require two or more antihypertensive medications (Mancia et al 2007 and Chobainan et al 2003). Clinical evidences from certain studies advocate using combination drug for initial therapy if there is a 20/10 mm Hg elevation in BP above goal (BP is >160/100 mm Hg for patients with uncomplicated hypertension or >150/90 for those with diabetes and other co-morbid conditions) (Chobanian AV et al 2003; Williams B et al 2004). Since blood pressure is result of several physiological mechanisms, thus an attempt to block one (as in monotherapy) tends to increase compensatory activity of others. Two drugs from different classes with complimentary mechanisms of action may result in additional BP decreases compared with either agent used alone. In a recent meta-analysis, Wald and colleagues (Wald et al 2009) showed that the combination of drugs from two different antihypertensive classes was up to 5

times more effective in lowering BP than increasing the dose of one drug. Hypertensive patients whose BP is not controlled adequately by monotherapy amlodipine 5 mg may therefore benefit from combination therapy by adding an antihypertensive agent with a distinct and complementary mechanism of action. There are published data suggesting that the combination of a calcium channel blocker (CCB) with an angiotensin II receptor blocker (ARB) is beneficial (Barrios et al 2009). Furthermore, such approach of adding a blocker of the renin-angiotensin system (RAS) to a CCB appears to be associated with a reduction in the incidence of CCB-related edema (Fogari et al 2007). The exact mechanism for this attenuation of edema remains to be established but appears to involve the ability of RAS blockers to counteract the microcirculatory changes induced by CCBs and dilate venous capacitance vessels (kohlmann et al 2006).

Fixed dose combination (FDC) of Telmisartan and Amlodipine also satisfied the criteria of rational use of medicines. The Rational Use of Medicines (RUM) is defined as "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community". Thus, rational use of medicines means need-based use of them keeping in mind the pathological status, therapeutic indices, drugs interactions and adverse drug reactions (Ray et al 1999).

The rationality of FDCs should be based on certain aspects such as (Sen 2002):

- The drugs in the combination should act by different mechanisms.
- The pharmacokinetics must not be widely different.
- The combination should not have supra-additive toxicity of the ingredients.

In present study, results of Telmisartan and Amlodipine combination were in coherence with the above mentioned standards of rational fixed dose combination.

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, low-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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