Original Article

Are all fixed dose combinations equally effective in blood pressure control? The analysis of four different fixed dose antihypertensive combinations

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ABSTRACT

Objective: Hypertension guidelines recommend the use of fixed dose combinations as the first step treatment in patients with stage 2 and 3 hypertension. The aim of this study was to compare the antihypertensive effects of four different fixed-dose preparations containing beta blocker (BB)-diuretic, ACE inhibitor (ACEI)-diuretic, angiotensin receptor blocker (ARB)-diuretic, and calcium channel blocker (CCB)-ACEI.

Methodology: Eighty patients with newly diagnosed hypertension whose sitting blood pressure (BP) ≥ 160/100 mmHg were randomized to receive either of those four fixed dose antihypertensive preparations: atenolol 50 mg-hydrochlorotiazide (HCTZ) 12.5 mg, or lisinopril 20 mg-HCTZ 12.5 mg, or telmisartan 80 mg-HCTZ 12.5 mg or verapamil 180 mg- trandolapril 2 mg. All the patients were followed up for six months.

Results: Both systolic BP (SBP) and diastolic BP (DBP) were reduced similarly in all groups (45.7/22.4 mmHg in BB-diuretic group, 45.8/18.1 mmHg in ACEI-diuretic group, 54.6/17.6 mmHg in ARB-diuretic group and 38.9/16 mmHg in ACEI-CCB group. For SBP p=0.19 and for DBP p=0.43).

Conclusion: All investigated fixed dose antihypertensive combinations were found similarly effective in reducing blood pressure.

KEY WORDS: Fixed dose combination, Beta blocker, ACE inhibitor, Angiotensin receptor blocker, Calcium channel blocker, Diuretic.

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INTRODUCTION

Fixed-dose combinations are increasingly used in clinical practice in order to achieve the therapeutic goals. Hypertension guidelines recommend the use of fixed dose combinations as initial therapy in patients with stage 2 and 3 hypertension.[1,2] Using combinations of agents with different action mechanisms provides antihypertensive synergy and also attenuates the possible side effects of each drug in monotherapy. [3,4] Although fixed-dose combination is more effective than either agent given as monotherapy, there is a deficiency of data comparing different fixed-dose combinations.

The purpose of this study was to compare the effects of fixed-dose preparations containing calcium

channel blocker (CCB) -ACE inhibitor (ACEI), ACEI- diuretic, angiotensin receptor blocker (ARB) - diuretic and ß-blocker (BB) - diuretic.

METHODOLOGY

Eighty patients with newly diagnosed hypertension whose sitting blood pressure (BP) ≥160/100 mmHg were included in the study. Secondary hypertension, known history of kidney disease, serious systemic disease, congestive heart failure, abnormal electrocardiographic findings or specific contraindication for a study drug and using antihypertensive medications were exclusion criteria. The study protocol was designed in accordance with Helsinki Criteria and was approved by local ethic committee of our hospital (12.02.2008 and Decision No: 44/H). Subjects provided written informed consent. BP was determined from a mean of three sitting measurements with an appropriate sized cuff as described in the Joint National Committee Report 7.[1] Patients were randomized into one of four groups. The patients received atenolol 50 mg plus hydrochlorothiazide (HCTZ) 12.5 mg in group 1, lisinopril 20 mg plus HCTZ 12.5 mg in group 2, telmisartan 80 mg plus HCTZ 12.5 mg in group 3, verapamil 180 mg plus trandolapril 2 mg in group 4. All the patients were followed up for 6 months.

Statistical analysis: All statistical analyses were made by using the software SPSS for Windows V13.0. Normality of distribution of variables was tested by Shapiro-Wilk and Kolmogorov-Smirnov tests. The Wilcoxon-Mann-Whitney U was used for comparison of two independent variables not distributed normally. The Kruskal Wallis test was used when we had one independent variable with two or more levels and an ordinal dependent variable. Data were reported as means ± SD. Significant differences were assumed for $p < 0.05$.

RESULTS

The study was completed with 52 patients (16 Males and 36 Females). Demographic and clinical characteristics of the patients were similar as listed in Table-I. In the BB-diuretic group three patients did not complete the study due to follow up loss, one patient had bradycardia and two patients did not complete the study because of hypotension. A total of six patients were unable to finish the study in BB-diuretic group. ACE I-diuretic group started with twenty patients and ended with thirteen patients. The reasons for discontinuation were; loss of follow up in two patients, diarrhea in one, cough in one, dizziness in one and hypotension in two. In the ARB-diuretic group five patients did not finish the study. One patient's treatment was

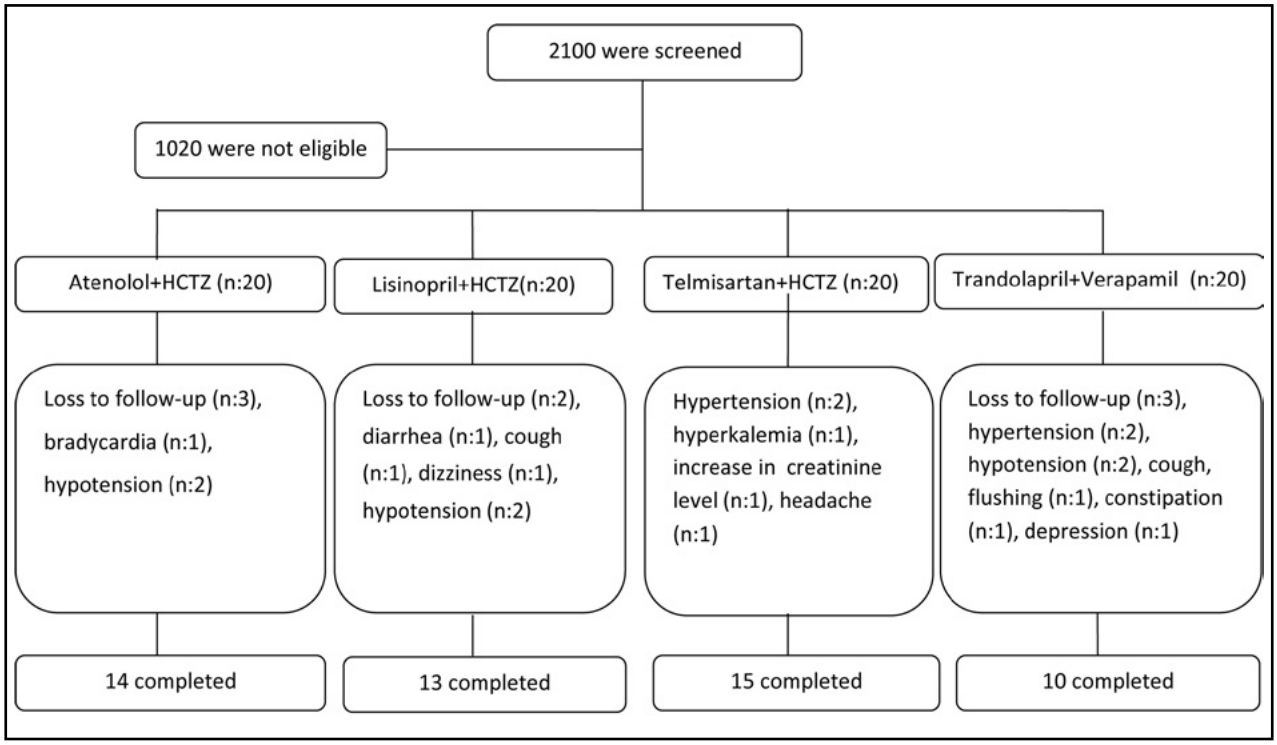

Fig.1: Flow diagram.

Table-I: Baseline characteristics of the study cohort.

	BB-diuretic n=14	*ACEI-diuretic n=13*	*ARB- diuretic n=15*	*CCB-ACEI n=10*	*p*
Sex (F)	78%	69%	62%	66%	0.82
Age (years)	51.9±9.4	53.1±7.0	56.4±9.3	48.1±11	0.18
Weight (kg)	78.1±11.7	86.9±13.2	87.3±19.7	81.7±9.8	0.38
Waist Circumference (cm)	101.4±13.7	103.0±14.2	106.2±12.9	103.7±6.7	0.7
SBP(mmhg)	174.4±12.1	169.2±13.5	178.3±14.4	163.9±9.9	0.055
DBP(mmhg)	100.4±9.5	96.9±4.7	99.3±10.9	97.1±5.5	0.35

stopped due to hyperkalemia. Two patients had continued hypertension therefore their treatment was altered. One patient had increase in his plasma creatinine level and one had headache. In the CCB-ACEI group; three patients did not finish the study due to follow up loss, one patient for depression, two patients for hypotension, two patients for continued hypertension, one patient for cough, and one patient for flushing, finally ten patients withdrew from the study. Discontinuation rates of groups were respectively; 30%, 35%, 25 % and 50%. (p=0.34) (Fig.1).

There was no difference in mean systolic and diastolic BP reductions between the groups (45.7/22.4 mmHg in BB-diuretic group, 45.8/18.1 mmHg in ACEI-diuretic group, 54.6/17.6 mmHg in ARB-diuretic group and 38.9/16 mmHg in CCB-ACEI group. For SBP p=0.19 and for DBP p=0.43) (Table-II).

DISCUSSION

Our study demonstrated that the four types of fixed dose antihypertensive combinations (BB-diuretic, ACEI-diuretic, ARB-diuretic and CCB-ACEI) were similarly effective in reducing Blood Pressure. Most of the studies compare fixed-dose antihypertensive combinations with monotherapy.[5,6] There are few studies which have compared a fixed combination with another fixed combination[7,8] which are usually dual comparisons.

In one of them, Fogari et al found a slightly greater reduction in ambulatory BP with telmisartan-HCTZ than lisinopril-HCTZ after six month period.[8] Our study did not confirm that finding as there was no difference between the BP lowering effects of lisinopril-HCTZ and telmisartan-HCTZ combinations. Bakris et al found similar BP reductions with CCB-ACE inh and ARB-diuretic combinations.[9]

BP control rates are very low all over the world; even in patients who are receiving antihypertensive treatment.[10] One rational of initial use of fixed dose antihypertensive combination is to raise the rate of BP control. The evidence-based recommendations for the prevention and management of hypertension suggest initiating combination therapy routinely in patients who require ≥ 20/10 mmhg blood pressure reduction to achieve target blood pressure.[11]

INVEST study[12] compared a calcium antagonist led strategy (verapamil SR-trandolapril) with a BB strategy (atenolol- HCTZ) for hypertension treatment and prevention of cardiovascular outcomes in coronary artery disease. Patients received individualized dose and drug titration following a flexible, multi-drug, guideline-based treatment algorithm, with the objective of achieving optimal BP control individualized for co morbidities. The strategies resulted in similar BP reduction and 70% of patients in both strategies achieved target BP levels (<140/90). With any of four different fixed dose antihypertensive combinations approximately three out of four patients (73.7%) achieved BP targets in our study.

Evaluation of discontinuation reasons reveals that; except follow-up losses, ACE-CCB was the most discordant group with 8 inadherences and followed by ACEI-diuretic and ARB-diuretic groups respectively. BB-diuretic group showed the most adherence. In this group the only reason of drop out

Table-II: Changes of sitting blood pressure in the 6th month.

	BB-diuretic	*ACEI-diuretic*	*ARB- diuretic*	*CCB-ACEI*	*p*
First SBP	174.4±12.1	169.2±13.5	178.3±14.4	163.9±9.9	0.055
Last SBP	128.6±11.0	123.5±6.3	123.7±10.4	125.0 ±22.4	0.45
Δ SBP	-45.7±13.9	-45.8±14.3	-54.6±17.7	-38.9±25.6	0.19
First DBP	100.4±9.5	96.9±4.7	99.3±10.9	97.1±5.5	0.35
Last DBP	78.0±9.4	78.8±14.6	81.6±21.5	81.1±9.3	0.54
Δ DBP	-22.4±9.8	-18.1±13.5	-17.6±24.2	-16.0±11.1	0.43

was a case of bradycardia . Two other losses were because of hypotension. Cough was one of the reasons of drop out in both ACEI-diuretic and CCB-ACEI groups. Hypercalemia and increase in creatinine levels that concern renal effects were seen in two patients treated with ARB-diuretic. However our study group was quite small.

Limitations of the study: A limitation of our study was the lack of biochemical and metabolic parameters which are closely related the selected antihypertensive medications. Also we did not compare the safety of different combinations. Absence of a group receiving a ACEI or ARB with a dihydropiridine CCB may also limit the conclusion about all currently popular fixed dose antihypertensive combinations.

In conclusion this study showed that there was no difference on BP lowering effect between four different type antihypertensive combinations and it was possible to reach BP control in more than two thirds of patients with any of those fixed dose antihypertensive combinations. Selection of antihypertensive combination for each patient should be individualized according to current hypertension guidelines.

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Authors Contribution:

***Banu Mesci, Aytekin Oguz, Selda Celik, Damla Coksert Kilic*:** Study design, acquisition of data, analysis and interpretation of data, drafting the article, revising it, final approval.

Murat Tekin, Gul Sagun, Mustafa Kemal Turgut: Acquisition of data, analysis and interpretation of data, revising the article, final approval.