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A prospective, randomized, open label experimental comparative assessment of the effect of amlodipine, atenolol, enalapril and thiazide in hypertensive patients

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Abstract
Aim: To compare the effectiveness of the four major antihypertensive drugs currently prescribed in health care setting to further the potential for evidence based prescribing practices.
Material and Methods: This study was conducted in Department of Pharmacology, ICARE Institute of Medical and Research & Dr. Bidhan Chandra Roy Hospital, Haldia, West Bengal, India, enalapril, amlodipine, and thiazide are the most commonly prescribed medications for essential stage I and stage II hypertension from their respective classes. A prospective, randomized, open label experimental study design was conducted over a period of one year in patients diagnosed with primary (essential) hypertension.
Results: Over a period of one year, a total of 100 patients were screened with 100 randomized across four treatment groups (i.e. Amlodipine, Atenolol, Enalapril and Thiazide). Twenty-five patients in each treatment group completed the follow up and entered to analysis. The mean (SD) baseline heart rate was 80.4 with no difference in distribution (p = 0.80). There was a significance difference in reducing SBP between Amlodipine (0.002) and Atenolol (p = 0.002). But there was no significant difference between Thiazide and enalapril (P = 0.67) There was no a significant difference in reducing DBP between amlodipine and thiazide (P = 0.82), amlodipine and enalapril (P = 0.66).
Conclusion: This study revealed that amongst the three drugs amlodipine followed by atenolol was found to be the most effective drug in reduction of systolic blood pressure. Thiazide and enalapril did not show a difference in reduction of mean blood pressure. Further, long term randomized trials are highly recommended to inform revision of hypertension treatment guidelines.

Keywords: amlodipine, hypertension, thiazide

Introduction

Blood pressure (BP) control is important in preventing the progression of cardiovascular damage in hypertensive patients [1]. However, it is difficult for a single class of antihypertensive drugs to achieve effective BP reduction in a majority of hypertensive patients [2, 3]. Therefore, combination therapies with two or more antihypertensive drugs are often required in the management of hypertension [4, 5]. However, in Japan, many patients with uncontrolled BP only receive one class of antihypertensives, [6] although combination therapy is encouraged.

One of the best combinations is that of a renin–angiotensin system (RAS) inhibitor and a low-dose thiazide diuretic because effectiveness and safety have been proven for them [7–9]. In a retrospective study that was conducted in older women, treatment with a combination of an angiotensin-converting enzyme (ACE) inhibitor and a thiazide diuretic showed a decreased probability of mortality from cardiovascular disease [10]. Recent reports suggest that the combination of a RAS inhibitor and diuretic can be useful even in diabetic [11] and very old [12] patients.

According to a recent systematic review, this attenuated effectiveness of BB and ACE-I may relate to low nitric oxide (NO) and high creatine kinase (CK) levels; however, other factors beyond pharmacokinetics were also associated such as genetic polymorphism, low renin levels, and a propensity towards 'salt sensitivity' amongst African-Americans as potential factors in the relatively poor response to ACE-I [13-14]. However, most conclusions were extrapolated from studies conducted in black people living in the United States and Europe, for which the outcomes may be affected by ethnic admixture and non-traditional lifestyles [15].

To our knowledge, there is no evidence which addresses the comparative effectiveness of these classes of drugs in a routine clinical practice. Therefore, the aim of this study was to determine the comparative effectiveness of these three drugs in northern Ethiopia to establish evidence and insights to inform future effective treatment of hypertension and guideline development.

Material and Methods

This study was conducted in Department of Pharmacology, ICARE Institute of Medical and Research & Dr. Bidhan Chandra Roy Hospital, Haldia, West Bengal, India from June 2013 to may 2014. enalapril, amlodipine, and thiazide are the most commonly prescribed medications for essential stage I and stage II hypertension from their respective classes. All inpatient and outpatient have departments to manage cases of hypertension and its complications. A prospective, randomized, open label experimental study design was conducted over a period of one year in patients diagnosed with primary (essential) hypertension.

Inclusion and exclusion: All patients diagnosed with stage I and stage II essential hypertension (Table 1), 18 years or older, and non-breast feeding, non-pregnant, and with no intention of pregnancy in the next three months met the inclusion criteria for this study. Patients experiencing a hypertensive emergency, having a known contraindicated to

any of the study drugs (e.g., ACE-I to patients with angio-edema), secondary hypertension diagnosis, or a major co-morbidity (i.e., diabetes mellitus, kidney disease, heart failure, stroke, or coronary artery disease), or a body mass index greater than 40 kg/m^2 were excluded.

Table 1: The stages of hypertension according to JNC- 7 [16]

Stage of hypertension	SBP	DBP
Normal	90–119	60–79
Pre-hypertension	120–139	80–89
Stage I	140–159	90–99
Stage II	160	100

The formula for sample size determination was $n = (Z\alpha_{/2}+Z\beta)^2\ 2\sigma^2 / d^2$, assuming the sample size is equally distributed across the groups, where $Z\alpha_{/2}2$ for a confidence level of 95 %, α is 0.05 and the critical value is 1.96, Zβ for a power of 80%, β is 0.2 and the critical value is 0.84, σ^2 is the population variance, which is assumed to be equal across the groups, and d is the difference we would like to detect which is 5 mmHg and assuming 10% for loss to follow up and withdrawal. First we calculated the sample size required for each drug by using the above formula and then we took the maximum sample size from the three calculated numbers and multiplied by three, yielding a required sample size of approximately 100. This was allocated to each group as 1:1:1.

After the patients were screened for eligibility, drugs were randomly assigned to each patient by a senior physician randomly. The method was simple randomization, using random generated numbers. When the patient appeared to the study hospitals the drugs were assigned to either of the three medications randomly. We did not make an attempt to alter the medications to make them identical and indistinguishable to the patients, partly because of feasibility and cost, as well as the aim of this study was to assess the effectiveness of these drugs in routine clinical practice. The drugs were prescribed to the patients randomly since the guidelines indicate that a patient with essential hypertension can take any of the three drugs.

Outcome and treatment

The primary outcome (dependent variable) was mean reduction in BP as it is the best measure to predict cardiovascular outcomes. It was calculated as the difference between BP value in each follow-up after starting therapy and baseline BP; thus, the average of the difference was the mean reduction in BP (SBP and/or DBP). Secondary outcomes considered included time to cardiovascular events such as heart rate as well as renal functions. The independent variable considered was treatment type, representing three drugs (i.e., amlodipine, antenolol, thiazide and enalapril) from the three classes.

One clinical pharmacist, one resident physician, and a senior physician, were assigned for data collection and follow up. Recruitment and collecting baseline information was carried out by one resident when patients diagnosed with hypertension and appeared in the cardiology, inpatient internal medicine, and/or outpatient departments of the study hospitals.

Ethical consideration: Ethical clearance was obtained from the Ethical Review Board. Written informed consent was obtained after of the purpose of the study. Anonymity and confidentiality of patients were maintained.

Results

Over a period of one year, a total of 100 patients were screened with 100 randomized across four treatment groups (i.e. Amlodipine, Atenolol, Enalapril and Thiazide). Twenty-five patients in each treatment group completed the follow up and entered to analysis.

Overall, the three groups were fairly balanced in all characteristics (Table 2). The majority of the participants were females, 66, married (70), and had education till 1-8 grade (53).

The overall mean (SD) age of patients was 56.7(14.8) the mean of baseline SBP was 164 and there was a significant difference in distribution between the study drugs (P = 0.005); whereas the mean DBP was 96 with a similar distribution across the groups (P = 0.42). The mean (SD) baseline heart rate was 80.4 with no difference in distribution (p = 0.80). (Table 2)

On bivariable analysis using ANCOVA of all socio-demographic and clinical variables, baseline SBP (P = <0.001) and DBP (P = 0.006) was significantly associated with mean reduction in BP. Other variables did not have significant association. There was a strong relationship between the baseline systolic hypertension on the mean reduction in SBP test after adjusted for drug groups, as indicated by a partial eta squared value of 0.58 which means 58% of variance in mean reduction of BP was explained by baseline SBP (Table 3).

Adjusted for baseline SBP and age those randomized Amlodipine, had significantly higher mean reduction in SBP. The mean reduction in SBP was -38.6 (-42, -32.1) in groups assigned to Amlodipine, -30.3 (-31.2, -25.8) in patients assigned to Atenolol, -31.4 (-34, -27.8) in patients assigned to Enalapril and -28.3 (-30.1, -27.5) in patients assigned to Thiazide. There was a significance difference in reducing SBP between Amlodipine (0.002) and Atenolol (p = 0.002). But there was no significant difference between Thiazide and enalapril (P = 0.67) (Table 4).

The mean reduction in DBP was -15.28 (-18.9, -12.1) in groups assigned to amlodipine, -14.7 (-16.2, -11.3) in patients assigned to atenolol, -14.2 (-15.8, -11.2) in patients assigned to enalapril and -14.80(-14.6, -11.0) in patients assigned thiazide. There was no a significant difference in reducing DBP between amlodipine and thiazide (P = 0.82), amlodipine and enalapril (P = 0.66) (Table 5)

Table 2: Baseline characteristics of study (N = 100).

Characteristics	Total (N=100)	Amlodipine (N = 25)	Atenolol (N = 25)	Enalapril (N = 25)	Thiazide (N = 25)	P-value
Sex						
Female (%)	66	25	12	16	13	0.40
Age, (mean ± SD)	54	53	53	56	57	0.11
Education (%)						
1–8 grade	53	22	16	11	4	0.32
9–12 grade	29	8	7	5	9	

College and above	18	7	2	3	6	
Marital status						
Married	70	30	19	13	8	0.82
Other	30	7	8	10	5	
Systolic BP, (mm Hg) mean (SD)	164	170.1	171.4	162.7	161.6	0.005
Diastolic BP, (mm Hg) mean (SD)	96	97.2	95.1	94.3	92.0	0.42
Heart Rate, bpm, mean (SD)	80.4	82.3	81.5	80.5	81.4	0.80
Creatinine, mg/dl, mean (SD)	0.8	0.73	0.71	0.77	0.82	0.22

Table 3: ANCOVA model test and effectiveness of drug types after adjusted for baseline BP and age

Source	Sum of squares	DF	Mean square	F-value	P-value	Partial ETA square
Model	173910	4	3571	40.2	<0.001	0.54
Intercept	52910.3	1	51820.2	52.7	<0.001	0.32
Baseline SBP	14302.8	1	13268.3	113.7	<0.001	0.58
Age	0.8	1	0.8	0.05	0.95	0
Drug type	1128.7	1	439.9	4.62	0.006	0.064
Error	11263.9	122	105.7			

Table 4: Adjusted mean reduction in SBP and mean difference between the study groups

Drug type	Comparator	Mean difference	Mean (CI) reduction SBP	P-value	95 %CI
Amlodipine	Enalapril	-8.82	-38.6 (-42, -32.1)	0.002	-10.2, -2.37
	Thiazide	-5.89		0.030	-9.37, -0.31
Atenolol	Amlodipine	8.33	-30.3 (-31.2, -25.8)	0.002	2.6, 10.4
	Thiazide	3.52		0.44	-2.4, 6.8
Enalapril	Amlodipine	-3.21	-31.4 (-34, -27.8)	0.30	-5.6, 2.5
	Atenolol	4.72		0.031	0.39, 9.30
Thiazide	Enalapril	-6.82	-28.3 (-30.1, -27.5)	0.22	-5.1, 2.3
	Atenolol	3.84		0.67	0.29, 8.71

Table 5: Adjusted mean reduction in DBP and mean difference between the study groups

Drug type	Comparator	Mean difference	Mean (CI) reduction SBP	P-value	95 %CI
Amlodipine	Enalapril	-0.80	-15.28 (-18.9, -12.1)	0.38	-3.2,2.3
	Thiazide	-1.41		0.29	-2.4,2.2
Atenolol	Amlodipine	0.81	-14.7 (-16.2, -11.3)	0.22	-2.1,3.4
	Thiazide	-1.44		0.25	-2.2,3.1
Enalapril	Amlodipine	-0.84	-14.2 (-15.8, -11.2)	0.38	-2.73,2.4
	Atenolol	1.29		0.40	-3.4,2.5
Thiazide	Enalapril	-0.83	-14.80(-14.6, -11.0)	0.77	-5.3, 2.2
	Atenolol	1.20		0.53	-4.1, 1.4

Discussion

The antihypertensive effects of RAS inhibitors are greatly enhanced with salt depletion. In fact, the addition of low-dose hydrochlorothiazide doubled the antihypertensive effect of losartan.16 similarly, hydrochlorothiazide greatly enhances the BP depressor effects of telmisartan [18-19]. Moreover, in mild-to-moderate hypertensive patients who did not respond to telmisartan monotherapy, the addition of low-dose hydrochlorothiazide effectively decreased BP in the first 4 weeks of use [19]. More importantly, the antiproteinuric effects of ACE inhibitors are blunted with salt excess, but the addition of hydrochlorothiazide suppresses the salt-induced increase in urinary protein [20]. Moreover, in the GUARD (Gauging Albuminuria Reduction with Lotrel in Diabetic Patients with Hypertension) trial [21], benazepril plus hydrochlorothiazide showed superior antialbuminuric effects relative to benazepril plus amlodipine. Thus, the combination of a RAS inhibitor and a thiazide diuretic may be beneficial, especially in hypertensive patients with kidney disease. In addition, the combination of a RAS inhibitor and a thiazide diuretic has been shown to be useful even in patients with type II diabetes mellitus [11] and in very old patients with hypertension [12].

Peterzan *et al* [22]. characterized the dose–response relationships for three commonly prescribed thiazide/thiazide-like diuretics, hydrochlorothiazide, chlorthalidone and bendroflumethiazide. He showed that chlorthalidone is more effective than hydrochlorothiazide both for BP reduction and biochemical outcomes. He also provided us the recommended dose and dose–effect relationship of these diuretics. In another large-scale meta-analysis published last year [23], thiazide-like diuretic could reduce risk of cardiovascular events and heart failure compared to thiazide-type diuretics. In this meta-analysis, the author used both placebo and other antihypertensive drugs as control arm, which would probably induce a biased baseline of the comparison. There was no detailed adverse effect analysis in this article. To avoid the difference in baseline, we only included studies that used both thiazide-like and thiazide-type diuretics as different arm but in the same trial. Additionally, this is the first meta-analysis, which highlighted the comparison of the major adverse effects of these two diuretics.

The Assessment of combination Therapy of Amlodipine/Ramipril (ATAR) study was an 18-week randomized prospective double-blinded Brazilian study which compared the combination of amlodipine and ramipril versus amlodipine monotherapy. The mean changes in ambulatory BP measurements were statistically significant between the combination versus the amlodipine monotherapy group, 18.7% vs 7.6%, p=0.011, respectively. In addition, the reported incidence of peripheral oedema was lower in the combination
Group [24].

The Candesartan and Diuretic versus Amlodipine in hypertensive patients (CANDIA) trial evaluated candesartan+ HCTZ combination versus amlodipine monotherapy [25]. This multicentre, double-blinded, randomized trial assessed patients with mild-to-moderate HTN not adequately controlled with monotherapy. After 8 weeks of therapy, there was no significant difference between the two groups. Systolic BP decreased by about 15

mm Hg; however, there was a higher discontinuation rate with amlodipine versus the combination drug due to peripheral oedema, 18% vs 6%, respectively. These findings suggest that while both agents are effective in lowering BP, the candesartan+HCTZ combination was better tolerated and hence may lead to better patient compliance [25].

The Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High blood Pressure (COACH) study was a study evaluating an ARB+amlodipine combination versus placebo. The 1940 patients in this 8-week treatment study showed achievement of BP goals (<140/90) with the combination therapy and again, a lower incidence of peripheral oedema [26].

These findings were echoed in the Telmisartan plus Amlodipine Study in amlodipine 5 mg (TEAMSTA-5), which tested another ARB+amlodipine combination. The study showed that the combination of telmisartan 40/80 mg plus amlodipine 5 mg was superior to amlodipine 10 mg monotherapy [27].

The mean reduction in SBP in the nifedipine group was higher compared to previous studies [28-29]; although lower compared to an earlier study which had included patients with BP of up to230/110[30] which found a SBP reduction of -58.5mmHg compared to our study -37 mmHg. Collectively, the effect of CCB in terms of mean reduction in SBP ranges from16.9mmHg [28] up to 21.15mmHg [31]. Regardless, nifedipine in our study was the optimal drug to reduce BP both in terms of measured change and in comparison to the other study drugs. This result was similar in DBP compared to previous studies [28, 31].

Conclusion

This study revealed that amongst the three drugs amlodipine followed by atenolol was found to be the most effective drug in reduction of systolic blood pressure. Thiazide and enalapril did not show a difference in reduction of mean blood pressure. Further, long term randomized trials are highly recommended to inform revision of hypertension treatment guidelines.

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