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Research Paper

A Short Term Comparative Study of Effects of Alpha-Adrenoreceptor Blocker (Terazosin) and Beta- Adrenoreceptor Blocker (Celiprolol) an Respiratory Parameters in Mild-To-Moderate Hypertensive Patients

Medical Science

KEYWORDS : Hypertension, Terazosin, Celiprolol, Angiotensin converting enzyme inhibitors diuretics, calcium channel blockers.

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ABSTRACT

Introduction: Angiotensin converting enzyme inhibitors (ACEIs), diuretics, calcium channel blockers (CCBs), α- blockers, β-blockers and Angiotensin receptor blockers (ARBs) are included in the list of first line agents for the management of hypertension. Terazosin is a long acting α- receptor blocker, devoid of first dose phenomenon, with improved pharmacokinetic profile and celiprolol (β-blocker) with an additional ISA at β2 adrenergic receptor & weak α2-adrenergic blocking property have comparable & favorable impact on hypertension.

Objective: To evaluate the effects of terazosin and celiprolol on respiratory parameters in mild-to-moderate hypertensive patients.

Method: A single blind prospective study was carried out at tertiary care teaching hospital. Hypertensive patients meeting the inclusion critertia were given terazosin 1 to 4 mg/day at bed time in group 'A' and celiprolol 200 to 400 mg OD daily in group 'B'. This strategy was followed for two weeks. Respiratory parameters were recorded before & after study period. Results obtained were analyzed statistically.

Results: A significant reduction in systolic as well as diastolic BP was seen in both groups. Respiratory parameters were not significantly altered with terazosin whereas FVC, FEV1 were improved significantly with celiprolol.

Conclusion: It is concluded that both the drugs terazosin & celiprolol have comparable antihypertensive effects. There was a significant improvement in respiratory parameters with celiprolol, which makes this agent valuable in patients with COPD/bronchial asthma.

Introduction

Hypertension is one of the commonest cardiovascular diseases. Blood pressure is classified as normal {systolic blood pressure (SBP) < 120 mmHg, diastolic blood pressure (DBP) < 80 mmHg}, prehypertension (SBP 120-139 mmHg, DBP 80-89 mmHg), stage 1 (SBP 140-159 mmHg, DBP 90-99 mmHg) and stage 2 (SBP ≥160, DBP ≥100). [1]

Adrenergic blockers have drawn attention due to their crucial role in the management of hypertension because of the dominant role of adrenergic mechanism in blood pressure. Angiotensin converting enzyme inhibitors (ACEIs), Angiotensin receptor blockers (ARBs), diuretics, calcium channel blockers (CCBs) and β-blockers constitute the mainstay of anti-hypertensive therapy; However α_1-blockers also have picked up a sufficient attention as useful antihypertensive agents because of their favorable impact on hypertension in term of quality of life, adverse effects profile and acceptance. [2 & 3]

Antihypertensive efficacy of selective α_1-blockers have been found equivalent to that of ACEIs, CCBs, Diuretics and β-blockers as observed in the treatment of mild hypertension study. [4] They are used either as monotherapy or can be effectively combined with diuretic, β-blockers or CCBs. [5] Fifth report of JNC [6] recommended these agents as a first line and report of second working party of the British Hypertension Society support this optimism. [7]

α_1-blockers are both arterio & veno-dilator. They block postsynaptic α_1-receptors on the vascular smooth muscle cells. This in turn prevents norepinephrine mediated vasoconstriction, leading to decrease in the peripheral resistance and thereby fall in BP. Thus α_1-blockers provide a rational means of reversing the pathophysiology of hypertension. The pre-synaptic α_2-receptors are not blocked by these agents; therefore devoid of reflex tachycardia, increased cardiac output and raised renin levels which are seen with the non-selective α_1-blockers (such as phentolamine), [8] Terazosin is α_1-blockers with improved pharmacokinetic profile & recognition of beneficial effects on lipid and glucose metabolism.

β- adrenergic receptor antagonists lower the blood pressure in patients with hypertension possibly by (1) inhibition of those β-receptors on the terminal neurons that facilitate the release of norepinephrine (pre-junctional β-receptors), (2) central nervous effects with reduction of adrenergic outflow and (3) lessening of the activity of the renin-angiotensin system, because the β-receptors mediate renin release. [9] Some β-adrenergic receptor antagonists contribute to lowering the blood pressure by their additional properties, i.e. α- adrenergic receptor blockade, β-adrenergic receptor agonism and mechanism(s) independent of adrenergic receptors. [10]

Conventional β-blockers have various adverse effects in hypertensive patients associated with airway disease, diabetes & peripheral vascular diseases. Celiprolol which have partial agonist activity expressed at β_2-receptor appears to be devoid of these problems. [11] It has additionally non-adrenergic receptor mediated vasodilating properties also, which contribute to decrease in peripheral resistance. [12]

Method:

Study population/ subjects:-

This prospective study was conducted over a period of two weeks. Patients who visited cardiology OPD and suffering from mild-to-moderate hypertension according to JNC-VI classification (SBP≥140 mmHg but <180 mmHg, and/ or DBP≥90 mmHg but <110 mmHg) were enrolled. Patients included in this study with age group of 30 to 70 years, who were able to perform clinical assessment and previously not treated. Patients excluded from this study were those suffering with advanced ichaemic

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heart disease, obstructive pulmonary disease, severe anaemia, disease of liver & kidney, known secondary hypertensive patients, unwilling patients, lactating or pregnant patients and women practicing any hormonal contraceptive preparation.

The study was approved by the institutional ethical review committee.

Study design:-
This single blind prospective study was conducted in a group of twenty patients meeting the inclusion criteria. The patients were initially enrolled into a one week run-in phase. They were instructed to take a regular diet (additional fat & salt intake were kept restricted). Those who completed this phase successfully and were still hypertensive entered the active treatment phase lasting for two weeks. They were randomly allocated to two groups i.e. group 'A' and group 'B' . In both the groups comprising of ten patients each, the dose was up-titrated in two steps, based on the response of the blood pressure to the medication. The maximum tolerated dose of drug was thus administered. At the end of the first week, if the BP normalized (SBP <140 mmHg & DBP<90 mmHg), or the DBP reduced at least by 10 mmHg, the patient was maintained on the same dose for the next week; if BP did not normalize & the fall in DBP was less than 10 mmHg, the patient was given a higher dose at the end of first week. Group 'A' was treated with terazosin in a dose of 1- 4 mg/day orally at bed time, whereas celiprolol was administered orally in the morning in a dose of 200-400 mg/day in group 'B' ; pre-treatment and post-treatment evaluation of respiratory parameters i.e. FEV1, FVC and PEFR were done. Results obtained were analysed by paired 't' test. Interdrug comparison was done by unpaired 't' test.

Results:
Age & sex wise distribution of subjects is shown in table-1. It is evident that both treatment groups were comparable in mean age (group 'A' = 55.6±8.64 year; group 'B' = 52.6±7.63 year). A total of 20 cases, out of which 13 patients (65%) were male and 7 patients (35%) were female. In group 'A' the male to female ratio was 1:0.66 and in group 'B', it was 1:0.44.

Before treatment the mean value of SBP & DBP in group 'A', was 159.4±7.37 mmHg & 101.6±4.40 mmHg (mean ±SD) and after two weeks of therapy it was 150.4±6.02 mmHg & 93.8±5.02 mmHg; it's mean of difference was -9.0 ±4.13 & -7.8±3.45 respectively. p<0.001, indicating significant improvement in BP with terazosin. It was also observed that in group 'B'; mean value of SBP & DBP before treatment was 159.4±11.11 mmHg, 99.6±3.37 mmHg (mean ±SD) and after treatment it was 142.4±10.05 mmHg & 87.2±3.27 mmHg (mean ±SD) respectively. It's mean of difference was -17.0±6.74 & -12.4±4.08 respectively. It's p value was <0.001 for both SBP & DBP, showing that in group 'B', where therapy was started with celiprolol, there was highly significant reduction in BP. In intergroup comparison for SBP, p <0.01 and for DBP, it was <0.05 that means there was significant and greater reduction in SBP as well as DBP in group 'B'. (Table-2).

Baseline FVC (mean ±SD) L value was 2.26±0.73 in group 'A' and after treatment it was 2.27±0.69 with mean of difference 0.01±0.10 (p>0.05). In group 'B' baseline FVC (mean ±SD) L value was 1.94 ±0.53 and after treatment it was 2.12±0.46 with a mean difference of 0.18±0.15 (p<0.01). In intergroup comparison, FVC was significantly increased in group 'B'.

Before treatment the FEV_1 (mean ±SD) L value was 1.63±0.84 & 1.72±0.44 and after treatment changed to 1.68±0.76 & 1.85±0.38 in group 'A' & group 'B' respectively. Their mean of difference was 0.05±0.15 & 0.13±0.13 in group 'A' & group 'B' respectively. The improvement in FEV_1 after treatment was significant (p<0.05) in group 'B' whereas it was non-significant in group 'A' (p>0.05).

The mean value of PEFR was 3.87±1.80 (mean±SD) L/Sec. & 4.12±2.43(mean±SD) L/Sec. at the beginning of therapy in group 'A' & group 'B' respectively. After therapy it was found 3.89±1.58 (mean±SD) L/Sec. & 4.18±2.33 (mean±SD) L/Sec. in both groups respectively with mean of difference in group 'A' was 0.02±0.48 & in group 'B', it was 0.69±1.01. In both groups, there was non-significant improvement in PEFR (p>0.05). (Table-3).

Discussion:
In present study, there was significant reduction in SBP and DBP after a short term therapy of two weeks in both the groups. Antihypertensive efficacy of terazosin as a monotherapy has been confirmed in various clinical trials. [13-16] It has been observed that a single dose of 0.5 mg terazosin reduces DBP whereas in higher doses upto 2 mg both SBP & DBP are reduced in normotensive healthy volunteers and hypertensive patients. [17 & 18] Results of present study are in accordance with Yajnik et al, who have studied the antihypertensive efficacy of celiprolol in mild-to-moderate hypertension in a subset of patients in India during short course therapy. There were statistically significant reductions in mean SBP & DBP from second week onwards. [19]

Pulmonary function tests in present study revealed no statistically significant alterations with terazosin , although a minor increase in the mean baseline values of FVC, FEV_1 and PEFR by 0.01±0.01, 0.05±0.15 and 0.02±0.48 respectively was observed (p>0.05 for all these parameters). This could be due to the fact that the bronchial musculature is devoid of α-receptors and therefore, α-receptors are not likely to affect the respiratory parameters. In present study, Celiprolol improved FVC by 0.18 L (p<0.01, very significant), FEV_1 by 0.13 L (p<0.05, significant) and PEFR by 0.69 L/Sec. (p>0.05 not significant). One of the major concerns with β-blockers use is attenuation of airway resistance and precipitation of bronchial asthma in susceptible individuals. Non-selective and even selective- β-blockers in higher doses are known to decrease FEV_1 significantly. These agents also antagonize β_2-mediated bronchodilation by terbutaline and salbutamol. In isolated preparation (guinea pig tracheal rings) celiprolol reversed the bronchoconstriction effect of serotonin and other bronchoactive substance. [20] Earlier it has been demonstrated that metoprolol in a dose of 100 mg could adversely affect the major respiratory functions whereas celiprolol upto 400 mg did not alter these. [21] Unlike propanolol and oxeprenol, celiprolol did not affect respiratory functions and did not antagonize the effect of salbutamol in ten patients with COPD and HT. [22] Pujet et al found that a single dose of 400 mg celiprolol increased FEV_1 by 12% whereas propranolol 40 mg reduced FEV_1 by 8% in a normotensive patients associated with stable asthma. These apparently positive respiratory effects of celiprolol were diminished when propranolol was co administered, suggesting that they were mediated by β-receptors. [23]

Conclusion: It can be concluded, that α and β blockers have comparable antihypertensive actions. Terazosin does not adversely affect the respiratory parameters and can be safely given to the patients of hypertension with concomitant COPD/ Bronchial asthma. However; celiprolol has an added advantage in such patients because of its additional partial agonistic activity at β_2 –receptors leading to an improvement in respiratory parameters.

Table-1:- Age & sex wise distribution of patients:

	Age range (mean±S.D.)	Male	Female	Total
Group A	55.6±8.64	6	4	10
Group B	52.6±7.63	7	3	10

Table-2:- Change in B.P. (mean ± S.D.) mmHg

	SBP		DBP	
	Group 'A'	Group 'B'	Group 'A'	Group 'B'
Pre-treatment	159.4±7.37	159.4±11.11	101.6±4.40	99.6±3.37
Post-treatment	150.4±6.02	142.4±10.05	93.8±5.02	87.2±3.27
Mean of difference	-9.0±4.13	-17.0±6.74	-7.8±3.45	-12.4±4.08
Paired 't'	6.875	7.96	7.14	9.60
p-value	<0.001	<0.001	<0.001	<0.001
Unpaired 't' & p-value	t=3.20, p<0.01		t=2.72, p<0.05	

Table-3: Change in respiratory parameters.

	FVC (mean±SD) L		FEV_1(mean±SD) L		PEFR (mean±SD) L/Sec.	
	Group 'A'	Group 'B'	Group 'A'	Group 'B'	Group 'A'	Group 'B'
Pre-treatment	2.26±0.73	1.94±0.53	1.63±0.84	1.72±0.44	3.87±1.80	4.12±2.43
Post-treatment	2.27±0.69	2.12±0.46	1.68±0.76	1.85±0.38	3.89±1.58	4.81±2.33
Mean of difference	0.01±0.10	0.18±0.15	0.05±0.15	0.13±0.13	0.02±0.48	0.69±1.01
Paired 't'	0.32	3.73	1.06	3.16	0.86	2.15
p - value	>0.05	<0.01	>0.05	<0.05	>0.05	>0.05
Unpaired 't' & p-value	t=2.98, p<0.01		t=1.28, p>0.05		t=1.82, p>0.05	

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