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Original Work

A comparative study to determine the clinical efficacy of Ramipril versus combination of Ramipril and Telmisartan in reducing microalbuminuria associated with grade 2 hypertension

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ABSTRACT: Inhibition of the renin-angiotensin system causes a reduction in urinary protein excretion. It is uncertain whether Angiotensin receptor blockers (ARBs) are equally effective antiproteinuric agents as Angiotensin converting Enzyme (ACE) inhibitors, or whether the combination of ACE inhibitors with ARBs is preferable to ACE inhibitor alone? Microalbuminuria is a prognostic marker for cardiovascular and renal risk. The objective of the study was to compare the clinical efficacy of Ramipril alone versus combination of Ramipril and Telmisartan by assessing the fall in B.P. and the improvement in the degree of microalbuminuria in stage II hypertensive patients. 60 patients of stage II hypertension without having any other cause of microalbuminuria were selected as subjects for the present study and were randomly distributed in to 2 groups- Group A included 30 patients who were given Ramipril 5 mg/ day and Group B included the same number of patients who were given a combination of Ramipril 5 mg/day and Telmisartan 40 mg/day. Baseline parameters included were measurement of Systolic, diastolic blood pressure and mean arterial pressure; microalbuminuria, blood urea, serum creatinine and serum potassium estimations. The drugs under trial were given for 20 weeks. Microalbuminuria was determined at 0 and 20 weeks. The mean percentage fall in microalbuminuria and mean arterial pressure were statistically highly significant ($p<0.0001$) with combination of Ramipril and Telmisartan (Group B) in comparison to Ramipril (Group A) alone. A highly significant ($p< 0.0001$) mean percentage increase in potassium level was observed in group B at the end of 20 weeks. The side effects were less observed in the combination group. Thus to conclude the combination of Ramipril and Telmisartan provides superior blood pressure (BP) lowering and target organ protection than Ramipril alone, hence the combination of Ramipril and Telmisartan is a better choice to treat and to prevent the progression of the disease.

KEY WORDS: ***Hypertension; Microalbuminuria; Ramipril; Telmisartan***

INTRODUCTION

Hypertension is a disease that affects about one billion individuals worldwide. It increases the risk for development of cerebral, cardiac, and renal events.[1] Many patients with essential hypertension may present with overt or sub-clinical target organ damage (TOD) involving the heart, kidneys, central nervous system or retina at the time of their initial diagnosis. The assessment of sub-clinical TOD has become the key element in evaluating hypertensive patients. Microalbuminuria (MA) is one of the earliest indications of kidney injury in patients with diabetes mellitus and hypertension and is associated with high incidence of cardiovascular

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morbidity.[2-7] MA possibly reflects a state of increased renal endothelial permeability and is considered an early marker of diffuse endothelial dysfunction[8-10]. Since reducing albuminuria delays the progression of complications, this parameter can be used as a benchmark for measuring the efficacy of therapeutic interventions.[11] Over the last few decades, the Renin Angiotensin system(RAS) has been a drug target of particular interest because of its involvement in cardiovascular and renovascular diseases. The two major classes of drugs that target the RAS are the Angiotensin-converting enzyme (ACE) inhibitors and the selective AT1 receptor blockers (ARBs).[12] Both ACE inhibitors and ARBs are effective antihypertensive agents that have been shown to reduce the risk of cardiovascular and renal events.

ACE inhibitors prevent the generation of Angiotensin II from Angiotensin I, while ARBs exert their vasodilatation effect at the receptor level by inhibiting the binding of Angiotensin II to the type I receptors. Ramipril is an ACE inhibitor while Telmisartan is a selective angiotensin receptor blocker. Inhibition of the renin-angiotensin system with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists is particularly effective at reducing the albumin excretion rate, but whether these classes of drugs are more beneficial in patients with microalbuminuria remains to be determined.[13]

The objective of the study was to determine whether Ramipril is an effective drug across a broad range of high-risk patients, or whether the combination of Telmisartan and Ramipril provides a more complete blockage of RAS, and provides greater therapeutic benefits especially in reducing microalbuminuria in hypertensive patients.

METHODOLOGY

This study was performed on 60 patients with essential hypertension having microalbuminuria attending the medical outpatient clinic and those admitted to the medical wards. Proven cases of secondary hypertension, pregnant women and those with diabetes mellitus, ischemic heart disease, renal disease, urinary tract infection, raised serum creatinine and macro proteinuria (albumin excretion more than 300 mg/24 hours), were excluded from the study. Informed consent was obtained from each participant.

Each participant was interviewed and examined in detail. The blood pressure of each participant was measured, using the auscultatory method with a standardized calibrated mercury column-type sphygmomanometer and a blood pressure above 140/90 mm Hg was regarded as hypertension. A detailed case record was prepared for each patient on a preformed study sheet. They were thoroughly examined for the presence of any other cause of microalbuminuria or other confounding factor.

The study subjects were randomly distributed into two groups - Group A comprised of subjects on Ramipril (5 mg/day) and Group B included the subjects on combination of Ramipril and Telmisartan (5mg and 40 mg/day respectively).

Patients were monitored first after one week and then at 2, 4, 8, 12, 16 and 20 weeks. The drugs under trial were given for a period of 20 weeks in both groups. In addition to the routine investigations, the study subjects underwent some special investigations such as Electrocardiogram (ECG), Chest radiography, Computed tomography (CT) of the brain and Echocardiography.

Microalbuminuria was assessed by urine albumin-creatinine ratio (ACR) based on the recommendations of the National Kidney Foundation and the American Diabetic Association.[14] The average ACR value from the three urine samples was determined. Urine albumin was estimated by turbidimetry. 5 ml of first-voided, early morning sample of urine was used. The patients were asked to avoid exercise prior to the urine collection. In women, urine examinations were done during the non-menstrual phase of their cycles. ACR value between 30-300 mg/day was taken as MA. Blood urea, serum creatinine and serum potassium levels were also estimated to assess the functional status of the kidney.

Results were tabulated in the form of mean and standard deviation, and analyzed by using student's 't' test and the level of significance were determined as 'p' values.

RESULTS AND DISCUSSION

The data from 60 patients who satisfied the inclusion criteria during the study period were analyzed (**Table 1**). There were 30 patients (16 male and 14 females) in each study group. The mean age in both groups A and B was 55.57 ± 6.45 and 58.67 ± 8.93 year respectively. The baseline levels of microalbuminuria in group A and B were-196.73 ± 54.40 mg/day and 166.83 ± 63.50 mg/day, respectively. The mean arterial blood pressure of group A was 128.89 ± 4.87 mm Hg while in group B, it was 129.38 ± 4.13 mm Hg. The differences in the baseline parameters were not statistically significant ($p > 0.05$) (**Table 1**).

In the present study, in group A, after treatment with Ramipril (5mg/day) for 20 weeks, (**Table 2**) there was highly significant ($p<0.0001$) fall in microalbuminuria (from 196.73 ± 54.40 to 125.93 ± 39.72), with mean percentage fall of 36.12% at the end of 20 weeks. These findings were consistent with the findings reported by other studies[15-18]. There was highly significant ($p<0.0001$) fall in mean arterial pressure from 128.89 ± 4.87 to 105.40 ± 3.39 with mean

percentage fall of 18.17 at the end of 20 weeks (**Table 2**). This effect was independent of the fall of microalbuminuria. The similar fall in mean arterial blood pressure has also been reported by various studies using various ACE inhibitors.[19-21]

During the course of treatment with Ramipril there was a significant ($p<0.01$) increase in potassium level at the end of 20 weeks. There was 4.29% increase in levels of serum potassium (from 4.03 ± 0.34 mmol/L to 4.21 ± 0.49 mmol/L), but none of the patients had levels more than 6.5 mmol/L (hyperkalemia). This increase in serum potassium is consistent with the other reported research studies and this rise could be due to the fact that ACEI by decreasing the synthesis of aldosterone, the main regulator of serum potassium, predispose to the development of hyperkalemia.[20,22]

There was highly significant fall in level of serum creatinine[21] but insignificant fall was observed in blood urea level during the course of treatment with Ramipril.

In group B, after treatment for 20 weeks, with combination of Ramipril and Telmisartan, (**Table 3**) there was highly significant ($p<0.0001$) fall in microalbuminuria (from 166.83 ± 63.50 to 62.40 ± 27.75), with a mean percentage fall of 63.19% at the end of 20 weeks.

The fall in microalbuminuria has also been reported to be significant to highly significant by various landmark studies using combination of ACE inhibitors and ARB[19-21].The percentage fall (**Table 4**) in microalbuminuria in the present study matched with the changes reported by these studies. With use of combination of Ramipril and Telmisartan, there was highly significant ($p<0.0001$) 20.79%percentage fall in mean arterial pressure (from 129.38 ± 4.13 to 102.47 ± 3.66) and this effect was independent of the fall in microalbuminuria. The fall in blood pressure has also been reported to be highly significant by various studies using combination of various ACE inhibitors and ARBs.[23] Highly significant increase in the level of serum potassium was also observed at the end of 20 weeks. There was 19.06 % increase in the level of serum potassium but none of the patients had levels more than 6.5mmol/L (hyperkalemia).[22] Significant fall in serum creatinine and blood urea level was also observed during the course of treatment with combination therapy.[21]

As a whole the study was uneventful and none of the patients had serious side effects except for dry cough (8% in group A and 4% in group B), dizziness and headache (2% in both groups A and B). None of the patients had increase in serum potassium to the extent where medication needed to be stopped.

Table 1: Base line Characteristics of the subjects under study

Serial No.	Parameters	Group A		Group B		p- value
		Mean	S.D.	Mean	S.D.	
1.	Systolic blood pressure(mm Hg)	169.87	7.08	170.67	6.71	>0.05
2.	Diastolic blood pressure(mm Hg)	108.40	4.28	108.73	4.53	>0.05
3.	Mean Arterial blood pressure	128.89	4.87	129.38	4.13	>0.05
4.	Microalbuminuria (mg/day)	196.73	54.40	166.83	63.50	>0.05
5.	Serum Creatinine (mg%)	1.07	0.16	1.15	0.23	>0.05
6.	Blood urea (mg%)	33.88	9.80	35.91	8.44	>0.05
7.	Serum Potassium (m.mol/L)	4.03	0.34	3.89	0.24	>0.05

Table 2: Effect of Ramipril on microalbuminuria, mean systolic blood pressure, mean diastolic blood pressure, mean arterial pressure, serum potassium, serum creatinine and blood urea levels in Group A patients

Serial No.	Parameter	Base Line (Mean ±SD)	After 20 weeks (Mean ±SD)	p- Value
1.	Micro Albuminuria(mg/day)	196.73±54.40	125.93±39.72	<0.0001
2.	Mean Systolic Blood Pressure(mmHg)	169.87±7.08	138.20±5.26	<0.0001
3.	Mean Diastolic blood pressure(mmHg)	108.40±4.28	89.00±3.74	<0.0001
4.	Mean Arterial Pressure(mmHg)	128.89±4.87	105.40±3.39	<0.0001
5.	Serum Potassium (m.mol/L)	4.03±0.34	4.21±0.49	<0.01
6.	Serum Creatinine(mg/dL)	1.07±0.16	1.00±0.13	<0.001
7.	Blood urea (mg/dL)	33.88±9.80	32.22±6.13	>0.05

Table 3: Effect of combination therapy (Ramipril and Telmisartan) on microalbuminuria, mean systolic blood pressure, mean diastolic blood pressure, mean arterial pressure, serum potassium, serum creatinine and blood urea levels in Group B patients

Serial No.	Parameter	Base Line (Mean ±SD)	After 20 weeks (Mean ±SD)	p- Value
1.	Micro Albuminuria(mg/day)	166.83±63.70	62.40±27.75	<0.0001
2.	Mean Systolic Blood Pressure(mmHg)	170.67±6.71	135.53±5.67	<0.0001
3.	Mean Diastolic blood pressure(mmHg)	108.73±4.83	85.93±4.83	<0.0001
4.	Mean Arterial Pressure(mmHg)	129.38±4.87	102.47±3.66	<0.0001
5.	Serum Potassium (m.mol/L)	3.89±0.24	4.65±0.55	<0.01
6.	Serum Creatinine(mg/Dl)	1.15±0.23	1.05±0.17	<0.001
7.	Blood urea (mg/dL)	35.91±8.44	34.75±8.52	<0.01

Table 4: Comparison of effect of Ramipril (Group A) and combination therapy -Ramipril and Telmisartan (Group B) on various parameters in study subjects after 20 weeks of therapy

Serial No.	Parameter	Group A (Mean ±SD)	Group B (Mean± SD)	p- Value
1.	Mean % fall in Micro Albuminuria	36.12±8.31	63.19±9.23	<0.0001
2.	Mean % fall in Systolic Blood Pressure(mmHg)	18.59±2.62	20.53±3.32	<0.05
3.	Mean % fall of Diastolic blood pressure(mmHg)	17.82±3.86	20.97±2.96	<0.001
4.	Mean % fall of Arterial Pressure(mmHg)	18.17±2.68	20.79±2.02	<0.0001
5.	Mean % rise in Serum Potassium (mmol/L)	4.20±6.65	19.06±8.46	<0.0001
6.	Mean % fall in Serum Creatinine(mg/dL)	6.01±10.39	7.14±8.50	>0.05
7.	Mean % fall in Blood urea (mg/dL)	2.50±12.38	3.31±5.84	>0.05

Microalbuminuria is frequently accompanied by hyperfiltration and anticipates a decline in renal function,[24] hypertensive microalbuminuria is characterized by unchanged glomerular filtration rate, reduced renal plasma flow, increased filtration fraction, elevated vascular resistance[25-28] and exhaustion of the renal functional reserve.[29]

The ACE inhibitors reduce RAS activation by blocking the conversion of Angiotensin I to Angiotensin II, leading to decreased activation of both AT1 and AT2 receptors. Angiotensin II type 1 receptors predominantly mediate the pathological effects of Angiotensin II, including vasoconstriction and other mechanisms that raise blood pressure as well as vascular hypertrophy, endothelial dysfunction, atherosclerosis, inflammation, and apoptosis.[30] Angiotensin II type 2 receptors, in contrast, mediate mostly opposing and beneficial effects, promoting anti-proliferation, differentiation, regeneration, anti-inflammation, and apoptosis.

In addition to blocking the conversion of Angiotensin I to Angiotensin II, ACE inhibitors block the enzymatic degradation of bradykinin. Increased levels of bradykinin contribute to the positive effects of ACE inhibitors since activation of B2 receptor leads to release of nitric oxide, with vasodilatory and tissue protective results. In addition, evidence is accumulating that ACE itself can act as a cell-surface receptor and that binding of an ACE inhibitor to the enzyme triggers a signaling cascade that leads ultimately to PGI2 generation and additional vasodilatory effects.[31-33]

Many factors affect patients' compliance with therapy, one of which is tolerability of the treatment. The tolerability profile of ACE inhibitors is marked by a considerable incidence of cough, affecting up to 35% of patients.[34] The cough occurring with ACE inhibitor therapy is related to increased levels of kinins, and it is the most frequent reason for discontinuation of treatment with an ACE inhibitor.[35] Angiotensin-converting enzyme inhibition has also been associated with angio-oedema, which occurs much less frequently than cough (<1%). However, angio-oedema affecting the respiratory passages can be life-threatening.[36]

An additional disadvantage of ACE inhibition is that it reduces activity of the AT2 receptor along with the AT1 receptor. The functions of the AT2 receptor are generally opposed to those of the AT1 receptor; the AT2 receptor has anti-proliferative, pro-differentiation properties and mediates anti-inflammatory responses.[30] The ARBs block the

RAS by antagonizing the binding of Angiotensin II to the AT1 receptor. Because the ARBs are selective for the AT1 receptor, these agents have a greater potential for providing a complete inhibition of the RAS than ACE inhibitors.[37] In addition, ARBs have minimal affinity for the AT2 and thus permit activation of the AT2 receptor by Angiotensin II to proceed unopposed, possibly providing beneficial anti-proliferative and anti-inflammatory effects. It should be noted that the potential clinical significance of AT2 receptor-mediated actions is not universally accepted.[30]

Unlike ACE inhibitors, ARBs have no effects on bradykinin accumulation and do not induce NO and PGI2 via the B2 receptor. The clinical implications of this difference between the ARBs and the ACE inhibitors, aside from the absence of kinin-related cough with ARBs, are not known.[37] The ARBs have been associated with a highly favorable tolerability profile, better than that of any of the other classes of antihypertensive.[38]

Combination therapy with different classes of antihypertensive agents having complementary mechanisms of action has been shown in numerous studies to provide greater blood pressure reductions than either agent alone.[39] Although ACE inhibitors and ARBs both target the RAS, their mechanisms of action are complementary and have been shown to lower blood pressure to a greater extent when used in combination.[40,41] Adding an ARB to ACE inhibitor therapy may counter reactivation of angiotensin II and aldosterone escape during ACE inhibitor therapy by specifically blocking the AT1 receptor.[33,42]

Inhibitors of the renin–angiotensin system reduce proteinuria by decreasing the systemic arterial pressure and the intraglomerular filtration pressure and by changing pore size and charge of the glomerular filter[43-46]. Combining both drugs might therefore achieve more complete blockage of the renin-angiotensin system.

Proteinuria is not only a predictor of renal outcome, but also acts as a pathogenic factor for the progression of renal disease. Recent data suggest a linear relationship between reduction in urinary protein excretion and protection of renal function. Because proteinuria fulfills many criteria of a reliable surrogate marker, the additional reduction in proteinuria achieved by combining an ARB and an ACE inhibitor may be of direct relevance to the patient's renal prognosis.

CONCLUSION

The combination of Ramipril and Telmisartan provides superior blood pressure (BP) lowering and target organ protection than Ramipril alone, hence the combination of Ramipril and Telmisartan is a better choice to treat and to prevent the progression of the disease.

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