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The Beneficial Effect of Renin-Angiotensin-Aldosterone System Blockade in Treatment of Hypertension, Resistant to Conventional Antihypertensives, in Patients on Maintenance Hemodialysis

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Abstract

Background: Hypertension (HTN) is present in up to 90% of end stage kidney disease (ESRD) patients irrespective of the etiology of their kidney disease. Moreover, it is an important modifiable risk factor for progression to ESRD and its overall cardiovascular morbidity and mortality. **Objective:** to evaluate, prospectively, the role of Renin-Angiotensin-Aldosterone System blockade (RAAS) in HTN, resistant to 3 conventional antihypertensives, in patients on maintenance hemodialysis (MHD). **Patients and methods:** A total of 52 such patients were treated with Ramipril and 5 with Losartan after intolerable cough/shortness of breath following Ramipril-use. None of the patients had fluid depletion, renal artery stenosis and primary endocrinopathy. The study group was compared to a matched control group of MHD patients with normal blood pressure following 3 drugs-combination therapies. **Results:** All patients, with resistant HTN, had significant activation of RAAS system prior to treatment compared to inactive one in the control group. In those with resistant HTN, control of HTN, was established within 2 weeks of therapy and was associated with suppression of the RAAS. Such therapy was associated with minor side effects. **Conclusion:** Our study has shown that RAAS blockade is safe and effective in controlling such resistant HTN in MHD patients.

Keywords

ACEI, Aldosterone, Angiotensin, ARB, Hemodialysis, Hypertension, Renin,

Resistant Hypertension

1. Introduction

Hypertension (HTN) is the second leading cause of end-stage renal disease (ESRD) in the United States, and is present in up to 90% of ESRD patients irrespective of the etiology of their kidney disease [1]. It is recognized as an important modifiable risk factor for progression of chronic kidney disease (CKD) to ESRD as well as its overall cardiovascular morbidity and mortality [2]. In this patient population; the mechanisms responsible for HTN include: increased extracellular volume, renal-artery stenosis, increased sympathetic and renin-angiotensin-aldosterone system (RAAS) activation, abnormalities in properties of the vasculature such as endothelial cell dysfunction, increased oxidative stress, arterial stiffness, and exposure to exogenous mediators such as erythropoiesis-stimulating agents and dialysate [3]. In the current study, we prospectively, evaluated the role and safety of RAAS-blockade in hypertension, resistant to conventional-antihypertensives, in patients on maintenance hemodialysis (MHD).

2. Patients and Methods

During the period 1st January 2019 to 31st December 2022, ESRD patients with hypertension resistant to conventional antihypertensive treatment were included in the study. The study was conducted by Prof/ El-Reshaid's medical clinic and its affiliated dialysis centers. The clinic was established in 1997 in the center of Kuwait City and has adequate diagnostic and therapeutic facilities to care for out-patients and in-patients with its affiliated hospitals.

Inclusion criteria:

Patients were included if they had: 1) age ≥ 14 years; 2) MHD treatment for ≥3 months; 3) diastolic blood pressure (BP) ≥ 110 mm Hg, pre- and post-MHD, that was refractory to combination of adequate dosage of vasodilators, beta-blockers, and centrally-acting alpha2 agonist (resistant HTN); 4) euvolemic status; 5) lack of laboratory/radiological evidence of renal artery stenosis, cirrhosis and primary endocrinopathy; and 6) adequate compliance with drug-therapy and diet low in sodium and potassium. None of the female patients were menstruating or pregnant. Assessment of euvolemic state was established by clinical assessment, chest X-ray and BNP testing. Renal artery stenosis was excluded using adequate renal doppler ultrasonography. Related primary endocrinology (acromegaly, hyperthyroidism, reninoma, cushing's and pheochromocytoma) were excluded by hormonal testing and CAT scans for tumors in their respective sites.

Assessment of RAAS:

Measurements for renin and aldosterone levels were tested in a supine position for 1 hour prior to MHD session.

RAAS-blockade:

Since Ramipril is renally excreted; the starting dose was escalated gradually starting with 1.25 and up to 20 mg daily. The dose was titrated to achieve pre-MHD diastolic BP ≤ 90 mm Hg. If intolerable throat pain, cough or shortness of breath; Ramipril was replaced by Losartan. Its starting dose was 50 mg daily which was increased up to 100 mg daily to achieve target BP.

Control group:

It included patients who entered MHD program during the study period. Initially, they had significant HTN yet was amenable to therapy with the 3-drug combination. Except for their subsequent control of HTN; they had similar inclusion criteria to the MHD patients to resistant HTN.

Follow up:

Both groups were assessed clinically for HTN and drug side effects on subsequent MHD sessions. Moreover, laboratory tests that included serum electrolytes were done weekly. Six weeks later; renin and aldosterone levels were re-tested.

Statistical analysis:

SPSS statistical package version 25 was used for data entry and processing. The p-value ≤ 0.05 was used as the cut-off level for significance. Since all variables were normally distributed; they were expressed as mean ± SD and compared using a student's t-test. Comparison of changes with time, following therapy, was done using ANOVA test for repeated measures.

3. Results

A total of 57 MHD patients were included in the study. Five patients could not tolerate Ramipril for respiratory side effects yet had tolerated Losartan. The demographical profile of MHD patients with resistant HTN and their control group as well as their BP and hormonal profile at start and after 6 weeks of follow; is summarized in Table 1. The 57 study-population were whites at 49 ± 4 years, of whom 30(52%) were females. They started MHD 6 ± 1 months prior to inclusion time and had resistant HTN. At start, their systolic and diastolic values at 174 ± 19 and 115 ± 5 mm Hg, respectively. Moreover, they had high renin and aldosterone levels at 136 ± 7 and 1238 ± 140, respectively. However, their Aldosterone/Renin ratio was normal at 9 ± 1.

Effect of RAAS-blockade:

In patients with resistant HTN; such treatment led to decrease in BP within 2 weeks of therapy. By 6 weeks; their systolic and diastolic BP were 129 ± 9 and 80 ± 5 mm Hg, respectively. By 6 weeks; repeat hormonal profile revealed significant increase of renin level to 383 ± 4 and decrease of aldosterone to 703 ± 9 indicating adequate RAAS-blockade. Both changes were significant at $p < 0.00001$.

Results in Losartan therapy:

The 5-patients group was similar in demography to the Ramipril group with 3 females (60%), age at 50 ± 3 years and 6 ± 1 durations of MHD and HTN therapy.

Table 1. Comparison between MHD patients with resistant HTN and their control groups.

Parameter	Patients	Control	Difference
Demographical data			
No	57	57	NS
Females/Males	30/27	29/28	NS
Age (years)	49 ± 4	49 ± 4	NS
Duration of MHD (months)	6 ± 1	6 ± 1	NS
Initial assessment			
Systolic BP	174 ± 19	173 ± 22	NS
Diastolic BP	115 ± 5	114 ± 6	NS
Renin	136 ± 7*	34 ± 5	0.00001
Aldosterone	1238 ± 140*	658 ± 114	0.00001
Aldosterone/renin ratio	9 ± 1*	20 ± 3	0.00001
Assessment (6 weeks later)			
Systolic BP	129 ± 9	131 ± 9	NS
Diastolic BP	80 ± 5	80 ± 5	NS
Renin	383 ± 4*	34 ± 3	0.00001
Aldosterone	703 ± 87*	660 ± 113	0.01
Aldosterone/renin ratio	2 ± 0*	20 ± 3	0.00001

N.B.: *Significant statistical difference ($P < 0.00001$) between initial assessment and 6 weeks later. Abbreviations: MHD: maintenance hemodialysis, HTN: hypertension, BP: blood pressure Normal hormonal tests ranges in supine position; Renin: 0.26 - 2.4 ng/L, Aldosterone: 80 - 440 pmol/L and Aldosterone/Renin ratio (pmol/ng): 15.7 - 41.9 (Females) & 10.3 - 23.7 (Males).

Their initial 1) HTN (systolic and diastolic) values and 2) hormonal levels (renin and aldosterone) were not different from Ramipril treatment-group. Moreover, their response to therapy (HTN and hormonal levels) was not different from the Ramipril treatment group. Hence, on analysis, they were included in the RAAS treatment.

Side effects of therapy:

Despite dietary restriction and patient's compliance; minor increase in serum potassium was encountered in most patients. Few patients had required small amounts of calcium resonium on maintenance basis.

The control group:

It included hypertensive MHD patients with similar initial HTN that was easily controlled with conventional therapy. As seen in Table 1; they were matched for gender distribution, age, prior duration of MHD and initial HTN. Their hormonal profile showed mildly elevated renin yet normal aldosterone and aldosterone/renin ratio.

4. Discussion

The annual mortality in adult ESRD patients is nearly 20% with cardiovascular deaths being the leading cause [4]. In this patient population, hypertension is a major risk factor in its cardiovascular morbidity and mortality associated with cerebrovascular disease, peripheral vascular disease, LVH, congestive heart failure and coronary artery disease [5]. Unfortunately, it was controlled adequately in only 30% of patients with 12% untreated and 58% inadequately managed [1]. In the latter 2 groups; resistant forms were common. HTN was defined as resistant if > 140/90mmHg despite use of 3 antihypertensive medications of different classes at the best tolerated doses [6]. In patients on MHD, lack of compliance and fluid overload are major culprits [7] [8]. Moreover, renal artery stenosis and primary endocrinopathy are common [9]. In our study, we evaluated the role of activation of RAAS system in induction of resistant HTN in those patients. In our patients with resistant hypertension; RAAS system was significantly activated compared to those with controlled HTN who had mild activation (high renin). Moreover, its suppression, by Ramipril/Losartan had led to normotensive state. In patients on MHD; activation of RAAS, is multifactorial. A major factor was the poor perfusion (ischemia) of damaged kidneys since: 1) plasma renin, angiotensin I and II fell dramatically following bilateral nephrectomy in humans [10]; and 2) laparoscopic nephrectomy-controlled hypertension adequately in 8 patients while 3 had partial response and failed in 1 [11]. Subsequently, medical nephrectomy using Lisinopril, an ACEI, was tried in those patients. It controlled their 44-h ambulatory HTN [12]. Interestingly; further research in this field showed persistent activation of RAAS in some patients despite bilateral nephrectomy indicating that is not induced only by decrease renal perfusion by damaged kidneys [13]. Such phenomenon was attributed to: 1) increase in AII levels due to elevated ACE activity in injured pulmonary endothelial cells via complement activation [13]; 2) decrease in clearance of AII to Ang-(1-7)/Mas by decrease in ACE2 activity, especially in those with cardiovascular diseases, diabetes and liver disease [14]; and 3) genetic susceptibility to hypertension and glomerular progression to ESRD with the *ACE-DD* than with the *DI* and *II* alleles [15]. Moreover; up-regulation of angiotensin gene leading to enhanced intrarenal angiotensin mRNA has been observed in multiple experimental models of hypertension including angiotensin II-dependent hypertensive rats, Dahl salt-sensitive hypertensive rats, and spontaneously hypertensive rats as well as in kidney diseases including diabetic nephropathy, IgA nephropathy, and radiation nephropathy [16]. Such phenomenon of increase of intrarenal renin in addition to serum renin was observed in patients on MHD with decrease in prorenin and ACE expression and an increase in chymase, angiotensinogen and AT1R expression in the kidney may augment the intrarenal RAS activation and be associated with renal damage, even after initiation of dialysis [17]. Fortunately, Enalapril (an ACEI) was able to reduce such intrarenal renin by decreasing its T1 receptor stimulation [18]. Hence; despite the controversial issue of discontinuation of

RAAS-inhibitors in stages 3 and 4 of CKD with 1) beneficial effect on decline of GFR [19] and 2) deleterious effect on mortality and progression to ESRD [20] [21]; their use in stage 5 seems useful in our study.

5. Conclusion

RAAS-blockade is safe and efficacious in the control of resistant HTN and may improve morbidity and mortality inherent in this patient population.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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