THE EFFECTS OF ACE-I AND ARB ON PERITONEAL ALBUMIN LOSS AND SERUM ALBUMIN LEVELS IN PERITONEAL DIALYSIS PATIENTS

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ABSTRACT

Objective: Anti-proteinuric effects of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) have been established in various renal diseases. However, the effects of ACE-I and ARB on the permeability of peritoneal membrane are unknown and the effect of ACE-I and ARB use on peritoneal permeability in patients undergoing continuous ambulatory peritoneal dialysis has not been studied.

Methods: Fifty non-diabetic patients with high peritoneal permeability, who had been on a regular peritoneal dialysis (PD) treatment for at least one year, were included in the study. The patients were prospectively randomized either fosinopril 10 mg/day p.o (n=25) (group 1) or valsartan 80 mg/day p.o (n=25) (group 2) for 12 months. All patients received standard 35-cal/kg/day diets with 1.2-g/kg/day protein intake and strict salt restriction. All patients were on standard PD program (2 L; 1.36%, 4 exchanges/day). Annual mean serum albumin level, calculated from the monthly serum albumin level and peritoneal albumin values obtained from the dialysate after 8 hours, dwell on two occasions 6 months apart were measured twice yearly.

Results: A significant increase in the serum albumin values, (3.68±0.56 g/dl vs. 3.94±0.46 g/dl, $p<0.0001$) a significant decrease in peritoneal fluid albumin values (9.06±2.65 g/dl vs. 7.08±1.43 g/dl, $p<0.01$) were observed in the ACE-I group following the treatment. While no significant change (3.75±0.48 g/dl vs. 3.87±0.37 g/dl, $p>0.05$) was observed in the serum albumin values, a significant decrease (8.62±3.87 g/dl vs. 5.84±2.94 g/dl, $p<0.01$) was obtained in peritoneal fluid albumin values for the ARB group.

Conclusion: At the end of the study a significant decrease was observed in the peritoneal protein values for patients on ACE-I and ARB.

Key Words: Peritoneal dialysis, Angiotensin converting enzyme inhibitor, Angiotensin receptor blocker and albumin

INTRODUCTION

Abnormal excretion of protein in the urine has long been recognized as a marker of glomerular injury (1-3). Peritoneal protein leakage is the most common cause of functional transport abnormality from continuous ambulatory peritoneal dialysis (CAPD) in long-term

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peritoneal dialysis. During CAPD, various morphological changes take place in the peritoneum, including mesothelial denudation, interstitial fibrosis, neovascularization, and vascular alterations. Angiotensin-II (ANG-II) plays a role in stimulating macrophages and fibroblast-like cells to secrete TGFβ-1. A perivascular/interstitial fibrosis, for instance, accompanies chronic elevation in either circulating ANG-II or aldosterone (4) and, in case of ANG II, occurs in response to abnormal vascular permeability and the escape of macromolecules (5). These effects of ANG II in CAPD patients can be prevented by the same method described above for clinical studies, and peritoneal protein loss may be reduced.

MATERIALS AND METHODS

High and high-average transporter patients who have been on regular CAPD treatment for at least one year, who have not used any non-diabetic, essential amino acid and whose level of blood pressure was between 140-160/90-100 mmHg and daily urinary output between 50-300 cc were included in this study. Patients were selected by an open randomized method. Twenty- five patients were selected for fosinopril 10 mg, and 25 for valsartan 80 mg treatment. Before treatment, annual mean peritoneal albumin values were obtained for those patients on a diet of 35 cl/kg/day: (45% carbohydrate, 20% fat, 30% protein) and Standard PD program (2 L; 4 exchanges/day). Among the patients who used their medications for one year, who had an infection with a CRP level above 5 mg/l, who were identified to have additional volume during the visits and who could not comply with their medication and diet, and those who had to leave the standard dialysis program were excluded from the study. At the end of a year, while 23 of the patients on fosinopril completed the study, only 13 of the patients on valsartan did so. Serum and peritoneal albumin values were obtained by the method of spectrophotometry.

Statistical analysis: GraphPad was prepared by the Prisma V.3 packet program. Besides, the descriptive statistical methods (means, standard deviations) used in analysing data, a separate t test was used for comparisons between groups, and a paired t test was used for repeating measures of the groups. The results were evaluated for the significance level of $p<0.05$ with a confidence interval of 95%.

RESULTS

Twenty-two patients from the ACE-I group and 13 patients from ARB group completed the study. Three patients from the ACE-I group were excluded from the study, two for lack of compliance and one because of a peritonitis attack. In ARB group, 12 patients were excluded from the study; 6 for lack of compliance, 1 for active pulmonery tuberculosis, 2 for peritonitis, 1 for dental infection, 1 for insufficient dialysis due to leakage and for instrumental peritoneal dialysis, 1 for continuing additional volume. Table I demonstrates age and Body Mass Index (BMI) for the remaining patients.

Table I: Age and BMI comparison of each group.

	ARB (n=13)	ACE n=(22)	t	p
Age	44.38±13.65	47.59±14.47	- 0.64	>0.05
BMI	25.08±4.96	23.64±3.85	0.96	>0.05
BMI: Body Mass Index				

While no significant changes (3.75±0.48 g/dl vs. 3.87±0.37 g/dl, $p>0.05$) were observed in the serum albumin values, a significant decrease (8.62±3.87 g/dl vs. 5.84±2.94 g/dl, $p<0.01$) was obtained in peritoneal albumin values in the ARB group. After treatment, a significant increase (3.68±0.56 g/dl vs. 3.94±0.46 g/dl, $p<0.0001$) in the serum albumin values and a significant decrease in the peritoneal albumin levels (9.06±2.65 g/dl vs. 7.08±1.43 g/dl, $p<0.01$) were observed in the ACE-I group. (Figs 1-2)

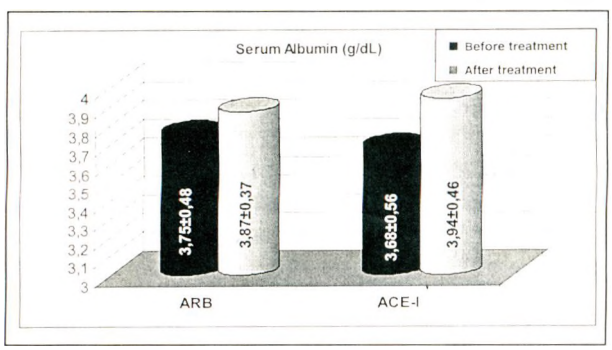

Fig. 1: Comparative values of serum albumin in both treatment groups before and after treatment.

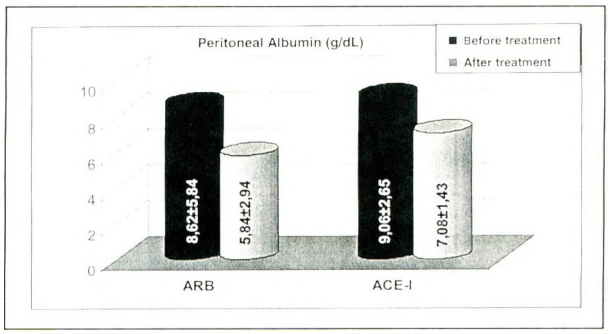

Fig.2: Comparative values of peritoneal albumin in both treatment groups before and after treatment.

The rate of exchange between pre and post-treatment serum albumin values in the ACE-I group was significantly higher than in that of the ARB group. In contrast, the rate of exchange between pre and post-treatment peritoneal albumin values in the ACE-I group was not significantly different than that of the ARB group (Table II).

Table II: Serum and peritoneal albumin exchange rates in both treatment groups

	ARB (n=13)	ACE I n=(22)	t	p
Serum Albumin	3.13±6.33	7.34±5.31	-2.08	<0.05
Peritoneal Albumin	26.92±26.06	16.64±28.18	0.98	>0.05

DISCUSSION

Remarkable antiproteinuric effects of ACE-I and ARBs, leading agents in antihypertensive treatment for the last century have been demonstrated in various clinical and experimental studies regardless of their blood pressure lowering effects (3,6-10). These agents have been used to prevent the vasoactive, proliferative, pro-oxidative, and permeative pathophysiological effects of ANGII treatment such as vasoconstriction, aldosteron release, sodium retention, hypertrophy in renal mesengial and tubulointerstitial cells, collagen accumulation, cardiac hypertrophy in cardiomiocytes and fibroblast and cardiac collagen accumulation, increased secretion by endothelium, increased release of vasopressin, facilitated sympathetic-adrenergic activation, facilitated supernoxide formation, increased level of plasminogen activator inhibitor-1, and accelerated gene expression (11,12).

A variety of morphological changes in the peritoneal membrane develop by similar mechanisms in patients undergoing peritoneal dialysis and lead to increased membrane permeability and thus to increased protein leakage into the peritoneal fluid. This is an unwanted situation for patients undergoing CAPD. The present study was conducted based on the idea that protein leakage of the peritoneal membrane could be decreased by use of ACEI and ARB regardless of their antihypertensive effects. At the end of the study a significant decreased was observe in the values for peritoneal protein.

At the end of the study, a significant decrease was observed in the peritoneal protein values in patients on ACE-I and ARB. While there was a significant increase in serum albumin values in the ACE-I group, a respective increase in the ARB group was not found to be significant. The large numbers of dropouts in ARB group and relatively smaller number of patients compared to the ACE-I group were considered to be responsible for this result.

In conclusion, ACE-I and ARB use in CAPD patients led to decreased loss of albumin into peritoneal fluid. The increase observed in the values of serum albumin in the ARB group failed to reach a significant level due to the decreased number of patients in this group. These results need to be supported by clinical and experimental studies involving a large number of patients.

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