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Research Paper

Management of High Blood Pressure and Left Ventricular Hypertrophy in Continuous Ambulatory Peritoneal Dialysis Patients with Low Dose of Spironolactone.

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ABSTRACT

Introduction: Blockade of the aldosterone effect with spironolactone is an approach that is being used more frequently in the treatment of hypertension and congestive heart failure. Objectives: The aims of our study were to prospectively describe trends in the left ventricular structure and function before and after spironolactone use, and to assess the safety of spironolactone use in peritoneal dialysis.
Patients and Methods: Thirty eight patients on continuous ambulatory peritoneal dialysis were selected for the study. All patients were adequately dialysed; with serum potassium levels less than 5.6 mmol/l. Eligible patients received spironolactone tablets 25 mg daily. Spironolactone tablets discontinued according to serum potassium. Echocardiography was performed at 6 and at 12 months. Biochemical, blood pressure and medication data were collected.
Results: Controlled blood pressure was achieved after 6 months ($p<0.001$) and 12 months ($p<0.001$) compared to the baseline. There was significant regression of interventricular septal thickness, left ventricular internal diameter and left ventricular wall thickness after 6 and12 months of spironolactone treatment ($p<0.0001$). The mean potassium level was 4.34±0.63mmol/l at baseline and 4.45±0.24 mmol/l at study completion ($p=0.24$). Gynecomastia was noted in one patient.
Conclusion: This study demonstrates that spironolactone therapy in continuous ambulatory peritoneal dialysis patients can be safe and may contribute to improved blood pressure control and cardiac function.

Key words: Dialysis, Spironolactone, Echocardiography, Left ventricle, CAPD, Peritoneal dialysis.

INTRODUCTION

Aldosterone has been identified in the last decade as an important contributor to the progression of both kidney and heart disease [1]. Anatomic abnormalities, including left ventricular (LV) hypertrophy and myocardial fibrosis are strong predictors of cardiac death in uraemic patients with heart failure and are more pronounced in dialysis patients compared with non-renal controls [2]. Echocardiographic assessment of LV mass has provided the best non-invasive information to permit diagnostic, therapeutic, and prognostic assessment of hypertensive heart disease [3,4]. Counteraction of the aldosterone effect with spironolactone is an approach that is being used more frequently in the treatment of hypertension and congestive heart failure. Dialysis patients are at risk of hyperkalemia, therefore the use of spironolactone is not common. Surprisingly, there is a lack of information in literature about the justification and use of spironolactone in peritoneal dialysis patients. This study was carried out prospectively to study trends in the left ventricular structure and function, blood pressure control after adding low dose of spironolactone use, and to assess the safety in continuous ambulatory peritoneal dialysis.

PATIENTS AND METHODS

The study was done in accordance with the principles of the Helsinki declaration. Medical Research Ethics Committee of the Ministry of Health approved the study protocol. Written informed consent (in Arabic) was obtained for each patient. The study was conducted during the period from October 2007 to May 2009.

Patients' selection and dialysis prescription

Thirty eight patients older than 18 years on continuous ambulatory peritoneal dialysis (CAPD) were selected for the study. All of them were having resistant arterial hypertension with a systolic BP of more than 140 mm Hg and a diastolic BP of more than 90 mm Hg. All CAPD patients performed four exchanges per day. Dialysis prescription for all patients was based on clinical and biochemical data. Most of the CAPD patients used 4 bags (2 L each] of peritoneal dialysis fluid containing 1.36 g/dl of dextrose, and 1 bag containing 3.36 g/dl dextrose daily. Treatments were carried out at their homes, by the patients themselves or by trained caregivers.
Compliant patients on CAPD for at least 6 months were selected for the study. All selected patients were adequately dialysed with KT/V >2 and serum potassium less than 5.6 mmol/l. Patients with valvular or congenital heart disease, unstable angina, hepatic failure, cancer, on ACE-I for a long duration, and non compliant patients to medication and diet instruction were excluded.

PROCEDURE

Spironolactone administration: Eligible patients were given 25 mg spironolactone daily. Spironolactone was decreased to three times weekly according to serum potassium and discontinued in severe hyperkalemia (>6 mmol/l). No changes were made to regular medications.

Echocardiography: Two dimensional echocardiographic studies were performed (General Electric Pass II.3.3 MHz transducer. General Electric Inc.) at 0 time, after 6 months, and 12 months. Interventricular septal thickness (cm), LV internal diameter at end of diastole (cm), and LV wall thickness (cm) were measured from LV short axis view with 2 dimensionally guided M-mode echocardiography. CBC, biochemistry and a standard 12-lead electrocardiography were done weekly for the 1 month, then bimonthly after.

Diet advice: All patients were on a low potassium diet. All patients were interviewed and diet advice was given by a dietician.

Statistical analysis: The Statistical Package for Social Sciences (SPSS) was used for data processing, using a cut-off level for significance at $p \leq 0.05$. The various descriptive statistics (mean, standard deviation) were used to describe the variables. Non-parametric Wilcoxon Signed Ranks test were used to find the association between two independent variables.

RESULTS

Patients' characteristics at entry into the study are summarized in table 1. Thirty eight patients were included in the study. Twenty six patients were females (68.4 %). The mean duration on CAPD was 16.39 ±13.11 months. Diabetic nephropathy was the most common renal disease among the studied patients.

Table 1: Demographic characteristics of the patients.

Mean Age (M±SD)years	55.84 ±12.51
Duration of on CAPD (Mean±SD) months	16.39 ±13.11
Gender, Number (%): Male	26(68.4)
Female	12(31.6)
Renal disease, Number (%)	
Diabetic Nephropathy	28(73.7)
Chronic Glomerulonephritis	4(10.5)
Chronic Tubulointerstial Disease	6(15.8)
Co morbidity: Number (%)	
Ischemic heart disease	20 (52.6)
Congestive heart failure	10 (26.3)
Cerebrovascular accident	2(5.3)
Hepatitis C/B	2(5.3)/1(2.6)
KT/V(Mean±SD)	2.25±0.44
BMI (kg/m^2)	29±3.25
Creatinine clearance L/1,73m2 on CAPD	87.7±25.8
UF rate mL/day	1205.5 ± 327.3
Residual renal function	21.6 ± 32.7
Peritoneal equilibration test (PET): Number (%)	10(10.5)
Low	14(36.8)
Low average	16(42)
High average	10(10.5)
High	11.3±1.7
Hemoglobin g/L (Mean±SD)	10.9±73
Medication prior to the study: Number (%)	
ACE Inhibitors	27(71)
β.Blockers	21(55.3)
calcium channels blockers	15(39.9)
digoxin	5(13.2)
nitrate	20(52.6)
statines	29(76.3)
iron therapy IV/Oral	4(10.5)/32(84.2)

Table 2 shows structure changes before and at 6 and 12 months after starting on spironolactone. There were significant changes in the interventricular septal thickness (cm), LV internal diameter at end of diastole (cm), and LV wall thickness (cm) after 6 and 12 months ($p<0.001$). Comparing the measurements of interventricular septal thickness (cm), LV internal diameter at end of diastole (cm), and LV wall thickness (cm) at baseline to those after 6 and 12 months showed significant differences ($p <0.001$).

Table 2: Left ventricular structure changes before and after Spironolactone.

	Baseline (A)	**After 6 month (B)**	**After 12 month (C)**	**P value A vs B**	**P value A vs C**
Interventricular septal thickness (cm)	1.20±o.25	1.10±0.21	1.03±0.10	<0.001	<0.001
LV internal diameter at end of diastole (cm)	6.06±0.68	5.20±0.68	5.04±0.58	<0.001	<0.001
LV wall thickness (cm)	1.27±o.22	1.08±0.19	1.02±0.12	<0.001	<0.001

Table 3: Blood Pressure in mmHg before and after Spironolactone.

	Baseline (A)	**After 6 month (B)**	**After 12 month (C)**	**P value A vs B**	**P value A vs C**
Systolic BP Median (Percentiles 25,75)	151.5 (140,156.2)	140 (138,143.5)	139.5 (136.7,140)	0.001	0.001
Diastolic BP Median(Percentiles 25,75)	79 (75,83)	75 (70,80)	74.5 (70,76)	0.001	0.001

As shown in table 3, there were significant reductions of systolic and diastolic blood pressure at 6 and 12 months when compared to the baseline ($p <0.001$)

Figure 1: Serum potassium during treatment.

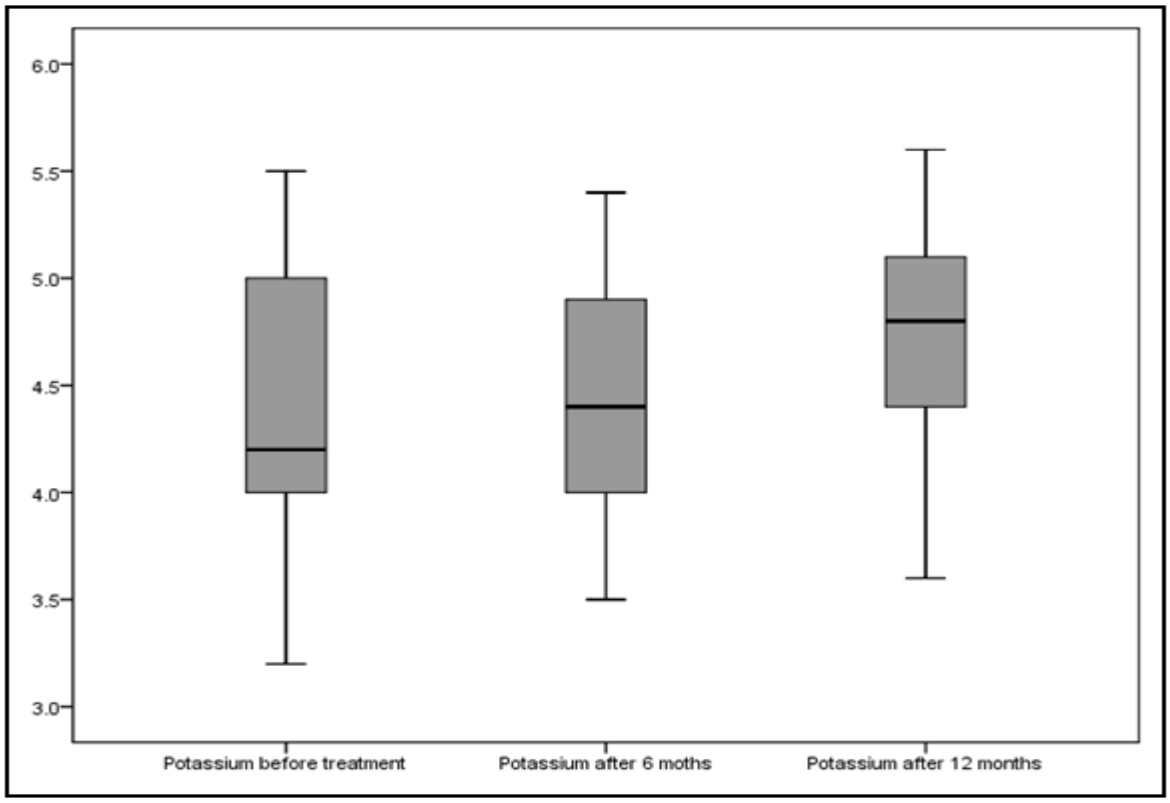

Figure 1 shows that the mean serum potassium level was 4.34±0.63 mmol/l at baseline and 4.66±0.62 mmol/l at study completion (not significant - p=0.24). The dose of spironolactone was discontinued in 3 out of 38 patients because of rising potassium. There was no electrocardiographic evidence of hyperkalaemia. Serum bicarbonate level (Median (Percentiles 25, 75) was significantly increased at 6 months, being 22.00 mmol/l (21.00, 24.00) and 12 months, being 22.00 mmol/l (21.75, 23.25), compared to baseline of 21.00 mmol/l (19.00, 23.00) (P<0.001).

DISCUSSION

Excessive activation of the renin–angiotensin–aldosterone (RAA) axis leads to myocardial hypertrophy and cardiac fibrosis; aldosterone mediates and potentiates the deleterious actions of angiotensin in animal models. Weber KT has shown that aldosterone is responsible for extensive scarring in the myocardial structure [5].

Spironolactone is a mineralocorticoid receptor antagonist that was shown to lower BP effectively in both general hypertensive patients and patients with primary aldosteronism. Spironolactone has shown improvement of LV function in patients with chronic heart failure (CHF)[6]. There is lack of information on spironolactone use in continuous ambulatory peritoneal dialysis (CAPD) patients. A first case report was published by Hausmann and Liel-Cohen [7] claiming the safety of aldosterone antagonism (25 mg spironolactone daily) in a 73-year-old diabetic patient with CHF on cycling PD. During 10 months of therapy, serum potassium did not exceed 5.1 mmol/l and both systolic and diastolic function significantly improved. This finding has been confirmed by Azar and colleagues [8] who reported a series of 15 patients with a certain degree of renal failure treated for CHF on Continuous Ambulatory Peritoneal Dialysis. In our study we observed significant regression of interventricular septal thickness, left ventricular internal diameter and left ventricular wall thickness after 6 and 12 months of spironolactone treatment. These findings were most likely linked to the reduction of myocardial fibrosis [9, 10].

Recently, it has been confirmed that low-dose spironolactone effectively reduces ACE activity and improves vascular function and other markers of prognosis (brain natriuretic peptide, collagen markers and QT interval length), even in patients with mild or asymptomatic heart failure [11]. Hyperkalemia is a major side effect of spironolactone. In our study however hyperkalemia has not been a significant complication in agreement with the Randomized Aldactone Evaluation Study (RALES) published in 1999 [12]. The lack of hyperkalemic episodes was attributed to the continuous character of PD treatment. On the contrary, hypokalemia may be a clinical issue in PD patients, due to efficacious dialysate potassium disposal and, possibly, malnutrition [13].

Another study also demonstrated that low-dose spironolactone with a low-potassium diet was safe. Serum potassium did not change significantly during a hemodialysis study period of 4 weeks, compared with the baseline and with controls, despite the fact that all patients were anuric and over half of them were concomitantly treated with ACEI or ARB [14].

The present study has also shown that the administration of spironolactone reduces systolic and diastolic blood pressure in anuric peritoneal dialysis patients. A possible explanation of this finding is that aldosterone mediates hypertension centrally [15, 16]. Hypertension and left ventricular hypertrophy occur in more than 70% of hemodialysis patients, and both contribute to morbidity and mortality [17-19]. In a recent study, spironolactone was administered for two weeks, reducing predialysis systolic blood pressure, but not producing hyperkalemia in oligoanuric hemodialysis patients [20]. Lack of a control arm in our study was a limiting factor. This was due to the lack of available patients fitting the inclusion criteria. Even though the limitations of our uncontrolled observational data are acknowledged, it is reliable when coming to assess the effect of spironolactone as added therapy for uncontrolled hypertension in peritoneal dialysis. As such, a unique approach to control blood pressure and to improve left ventricular function in peritoneal dialysis is provided.

CONCLUSION

This study demonstrates that low dose of spironolactone therapy in continuous ambulatory peritoneal dialysis patients can be safe. Spironolactone effectively improves blood pressure control and cardiac function. LV hypertrophy improved significantly after treatment. No significant rise of serum potassium was noted. More studies on a large scale are required to confirm the safety of spironolactone in peritoneal dialysis.

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