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Comparative study of enalapril *vs.* losartan on residual renal function preservation in automated peritoneal dialysis. A randomized controlled study

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ABSTRACT

Background. Residual renal function (RRF) is an important determinant of mortality and morbidity in patients receiving peritoneal dialysis (PD). Recent studies have shown a positive effect of angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) on RRF in PD patients. **Objective.** To compare enalapril and losartan for RRF preservation in automated peritoneal dialysis (APD) patients. **Material and methods.** An open label randomized controlled trial (RCT) with a 12 month follow-up period was conducted to compare the effect of enalapril vs. losartan on RRF preservation in 60 APD patients. Measurements were done at the start of the study (baseline), 3, 6, 9, and 12 months. A historical control group (HCG) without treatment was included to assess the natural history of RRF loss. **Results.** RRF in the enalapril group dropped from 3.65 ± 1.6 (baseline) to 2.36 ± 0.38 mL/min/l.73 m^2 (12 months). In the losartan group RRF was reduced from 4.1± 2.01 (baseline) to 2.54 ± 0.47 mL/min/ l.73m^2 (12 months). There were not significant differences between the two groups regarding RRF at 12 months. In the HCG, RRF declined from 3.68 ± 0.48 to 1.4± 0.29 mL/min/ 1.73m^2 (12 months). RRF in the HCG was significantly lower than RRF in the two treated groups at 12 months ($P < 0.05$). **Conclusions.** There was not significant difference on RRF preservation between enalapril and losartan groups. Comparing these results to those of the HCG suggests that the treatment with any of the drugs is useful in preserving RRF.

Key words. Residual renal function. ACE inhibitors. Angiotensin II blockers. Automated peritoneal dialysis. Randomized controlled trial.

Estudio comparativo de enalapril vs. losartán en la conservación de la función renal residual, en diálisis peritoneal automatizada. Ensayo clínico aleatorizado

RESUMEN

Antecedentes. *La función renal residual (FRR) es una determinante importante de mortalidad y morbilidad en pacientes tratados con diálisis peritoneal (DP). En estudios recientes se mostró un efecto positivo de los inhibidores de la enzima conversora de angiotensina (IECA) y de los antagonistas de los receptores de angiotensina II (ARA II) en la FRR en pacientes en DP.* ***Objetivo.*** *Comparar enalapril y losartán en la preservación de la FRR en pacientes en diálisis peritoneal automatizada (DPA).* ***Material y métodos.*** *Se hizo un estudio clínico aleatorizado (ECA) con periodo de seguimiento de 12 meses para comparar el efecto de enalapril vs. losartán en 60 pacientes en DPA. Las mediciones se hicieron al inicio del estudio, a los tres, seis, nueve y 12 meses. Se incluyó un grupo control histórico (GCH) sin tratamiento para valorar la evolución natural de la pérdida de la FRR.* ***Resultados.*** *En el grupo de enalapril la FRR se redujo de 3.65 ± 1.6 (basal) a 2.36 ± 0.38 mL/min/1.73 m^2 (12 meses). En el grupo de losartán la FRR disminuyó de 4.1 ± 2.01 (basal) a 2.54 ± 0.47 mL/min/1.73m^2 (12 meses). No hubo diferencias significativas entre los dos grupos en la FRR basal ni a los 12 meses. En el GCH la FRR disminuyó de 3.68 ± 0.48 (basal) a 1.4 ± 0.29 mL/min por 1.73 m^2 (12 meses). La FRR en el GCH a los 12 meses es significativamente menor que la FRR en los dos grupos tratados ($p < 0.05$).* ***Conclusiones.*** *No hubo diferencia significativa en la preservación de la FRR entre los grupos de enalapril y losartán. La comparación de estos resultados con los del GCH sugiere que el tratamiento con cualquiera de los dos fármacos es útil para preservar la FRR en pacientes en DPA.*

Palabras clave. *Función renal residual. Inhibidores de ECA. Bloqueadores de receptor de angiotensina II. Diálisis peritoneal automatizada. Estudio clínico aleatorizado.*

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) are recommended in peritoneal dialysis (PD) patients for hypertension or heart failure control.[1-3] Angiotensin II (AII) is an important factor in the development of renal fibrosis due to its hemodynamic effects on glomeruli and stimulation of extracellular matrix proteins synthesis, mediated by transforming growth factor-beta (TGFβ).[4-7] This may explain why treatment with ACEi and ARBs is renoprotective in patients with diabetic and non diabetic nephropathy.[8-12]

Treatment with ACEi and ARBs has been shown to be associated with decreased risk of residual renal function (RRF) decline in PD patients. The use of renin-angiotensin-aldosterone system (RAAS) blockade was independently associated with a 32% decrease in the development of anuria in patients with chronic kidney disease (CKD) irrespective of the dialysis modality.[13] A 70% decrease in mortality of PD patients treated with either ACEi or ARBs therapy has been shown.[14] It is tempting to speculate that the improved survival may have been related, at least in part, to preservation of RRF by the use of these agents.

It was shown that ramipril reduced the rate of RRF decline and delayed the development of complete anuria in prevalent continuous ambulatory peritoneal dialysis (CAPD) patients after 12 months. Average RRF declined 2.07 mL/min per 1.73 m^2. The difference between the average changes in RRF in the groups from baseline to 12 months was 0.93 mL/min per 1.73 m^2 (95% CI 0.09 to 1.78 mL/min per 1.73 m^2).[15] Another approach to inhibiting the RAAS is ARBs administration. It was demonstrated that RRF and daily urine volume were significantly better preserved in CAPD patients on valsartan (4.3 ± 0.7 to 3.4 ± 0.3 mL/min/1.73m^2) as compared to controls (5.9 ± 0.5 to 2.8 ± 0.4 mL/min/1.73m^2).[16] Although these two studies were small, they showed that drugs with renoprotective effects continue to exert benefits in patients with stage 1-4 CKD and slow the progression to anuria in stage 5 CKD patients on dialysis and thus should be continued in all patients in DP with RRF.[17]

Recently the time course of decline of RRF in 452 incident non anuric PD patients was followed-up for 3 years after the start of dialysis; one group of patients received ACEi/ARBs and the other was the control group. In contrast with previously published information, the time course of decline of RRF was not different between the 2 groups over the 3 years of PD treatment.[18]

In order to compare enalapril and losartan efficacy for RRF preservation in automated peritoneal dialysis (APD) patients, we conducted a randomized clinical trial (RCT) with a 1-year follow-up period. Unlike previously reported studies, our objective was to compare two good pharmacological options for RRF preservation in APD patients. We included a historical control group (HCG) of 30 patients in APD, in order to assess the natural history of RRF loss in 12 months without treatment.

MATERIAL AND METHODS

A prospective, open label, RCT was conducted. Sixty patients with APD as the initial renal replacement therapy for at least 1 year and RRF of at least 2 mL/min/1.73 m^2 were selected. Patients with infectious systemic disease, recurrent peritonitis, severe malnutrition, intolerance to ACEi or ARBs, and underlying medical conditions such as congestive heart failure, myocardial infarction, malignant hypertension and stroke within the preceding 6 months, were excluded.

Patients were randomly assigned to one of the two arms of the study. Assignment was in a 1:1 ratio by a computer generated list. After randomization, patients in one arm received ACEi (enalapril 10 mg/day), and those in the other arm ARBs (losartan 50 mg/day). RRF was measured as the mean of creatinine and urea clearances using 24 h urine collection and expressed as mL/min per 1.73 m^2. RRF was measured 5 times, at baseline, 3, 6, 9 and 12 months. At the time of enrollment all the patients had hematic count, glucose, blood urea nitrogen, creatinine, serum electrolytes (Na, K, Ca and P), peritoneal Kt/V and peritoneal creatinine clearance.

Sample size was calculated to test the hypothesis of a 2 mL/min/1.73 m^2 difference in RRF between the two arms favoring the enalapril arm,[15] a total standard deviation of 2.5, two sided $\alpha = 0.05$ and power $(1-\beta) = 0.80$. The calculated sample size was 30 patients per group (Power & sample size calculations. v 2.1.31 NJ, USA).

All the studied patients signed an informed written consent. The participating patients were recruited from the Hospital General ISSEMYM, in Naucalpan, Mexico. The Hospital's Clinical Research and Ethical Committee approved the study. On the basis of the sample size estimate, 60 stable patients receiving APD were included. Antihypertensive agents other than ACEi and ARBs were allowed. Doses were adjusted appropriately to achieve and maintain a 130/85 mm Hg target blood pressure. After randomization, patients were followed at 0, 3,

6, 9 and 12 months and RRF was measured at these times. A HCG of 30 patients in APD, was included in order to assess the natural history of RRF loss in 12 months without treatment.

The primary outcome measures were the longitudinal change in RRF and the time to anuria. Anuria was defined as total absence of urine output. Secondary outcome measures included peritonitis, duration of hospitalization for any cause, drug effects, cardiovascular events, nonfatal myocardial infarction, cerebrovascular events with permanent neurologic deficit and peripheral vascular disease requiring lower limb amputation above the ankle. Patients were asked open-ended questions about adverse events at each clinic visit.

Statistics

Data are presented as mean and standard deviation for continuous variables and as proportions for categorical variables. The analysis of the effect of enalapril and losartan on longitudinal changes in RRF and differences between the two groups were done by repeated measures of analysis of variance (ANOVA). The differences of RRF among the three groups were done by one way ANOVA. Kaplan-Meier estimator was used to analyze the probability of developing anuria in both groups. Chi-square test was used to analyze differences in hospitalizations and peritonitis. Statistical analyzes were done with SPSS v14 (SPSS Inc., Chicago, IL, USA). A p value of 0.05 or less was considered to be statistically significant.

RESULTS

Thirty patients were enrolled in each group; their baseline clinical characteristics are shown in table 1. There were not statistically significant differences in male: female ratio, age, weight, and height

Table 1. Baseline clinical characteristics and laboratory values in the two groups of patients.

Parameter	Enalapril	Losartan	p
N	30	30	NS
Age (years)	42.5 ± 18.5	49.2 ± 19.6	NS
Gender (female/male)	14 / 16	10 / 20	NS
Weight (kg)	62 ± 5	66 ± 8	NS
Height (m)	1.62 ± 5	1.68 ± 3	NS
BMI (kg/m^2)	25 ± 2.5	25 ± 3	NS
Systolic BP (mmHg)	130 ± 5	135 ± 10	NS
Diastolic BP (mmHg)	80 ± 10	70 ± 5	NS
Mean dialysis duration (years)	1.8 ± 0.6	1.5 ± 0.5	NS
Antihypertensive medication	30(100%)	30(100%)	NS
Prazosin	18(60%)	20(67%)	NS
β-blocker	12(40%)	10(33%)	NS
CKD diagnosis	NS		
Diabetes mellitus	12(40%)	14(47%)	NS
Nephrosclerosis	4(13%)	3(10%)	NS
Other or unknown	14(47%)	13(43%)	NS
Hemoglobin (g/dL)	10.5 ± 1	11 ± 2	NS
Hematocrit (%)	30 ± 1	31 ± 2	NS
Leukocytes (mm^3)	8000 ± 2000	9,000 ± 1,000	NS
Glucose (mg/dL)	140 ± 20	130 ± 10	NS
Albumin (g/dL)	3.8 ± 0.5	4 ± 0.2	NS
rGFR (mL/min)	3.65 ± 1.6	4.1 ± 2.01	NS
Proteinuria (g/24 h)	1.1 ± 0.2	1.3 ± 0.3	NS
Total Cr CL (L/week)	70 ± 2	69 ± 1	NS
Total Kt/V	1.95 ± 0.1	2 ± 0.2	NS
UFR (L/24 h)	1 ± 0.2	l.l ± 0.3	NS

BMI: body mass Index. BP: blood pressure. NS: non-significant. rGFR: residual glomerular filtration rate. Total Cr Cl: total weekly creatinine clearance. UFR: Ultrafiltration rat.

between the groups. Blood pressure at baseline and the cause of CKD were not different between the groups. There were similar numbers of diabetic patients in the two groups. The baseline laboratory tests results were similar in both groups (Table 1). The 30 patients in HCG had 48 ± 7.2 years, gender: 12 women/18 men and the time in dialysis was 1.7 ± 0.5 years, similar clinical characteristics with the other two groups ($p > 0.05$).

Baseline renal function and dialysis adequacy indexes are shown in table 1. The two groups showed similar result of PD adequacy, including Kt/V, ultrafiltration rate and weekly creatinine clearance. RRF gradually declined during the study period in both groups (Figure 1). RRF was similar at baseline in both groups, 3.65 ± 1.6 in the enalapril group and 4.1 ± 2.01 mL/min/1.73 m^2 in the losartan group (ns). At 6 months, RRF was 3.0 ± 0.5 in the enalapril group and 3.14 ± 1.6 mL/min/1.73 m^2 in the losartan group (ns) and at 12 months RRF was 2.36 ± 0.38 in the enalapril group and 2.54 ± 0.47 mL/min/1.73 m^2 in the losartan group (ns). RRF declined by 1.29 ± 1.21 in the enalapril group compared with 1.56 ± 1.54 mL/min/1.73 m^2 in the losartan group (ns). The average decline in RRF in patients receiving losartan was 0.27 mL/min/1.73 m^2 less than that in enalapril group (ns) (Figure 1).

RRF in the HCG at baseline was 3.68 ± 0.48 mL/min/1.73m^2 which was not different from baseline values in the enalapril and losartan groups. At 12 months it dropped to 1.4 ± 0.29 mL/min/1.73m^2 ($p < 0.05$ *vs*. RRF at 12 months in the enalapril and losartan groups) (Table 2).

There were not differences in the number of patients developing anuria between the two groups; 11 patients were anuric at the end of the study in the enalapril group and 12 patients in the losartan group (Figure 2). Urinary volume in the enalapril group was 653 ± 243 mL/d and in the losartan group was 798 ± 353 mL/d (ns). Proteinuria at the beginning of the study was 1.1 ± 0.2 g/24 h

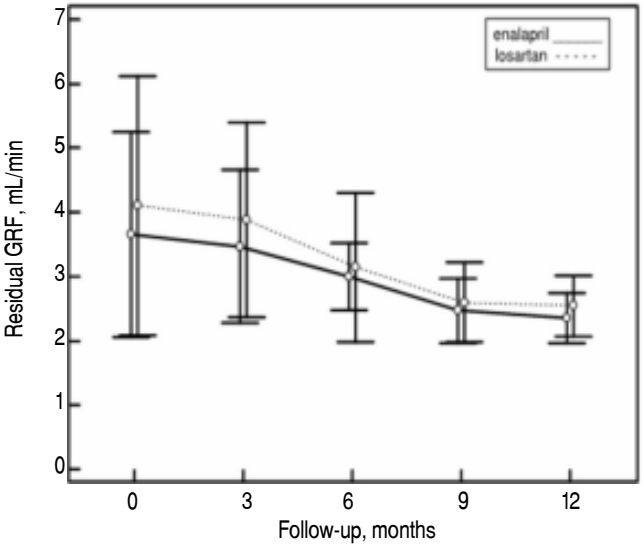
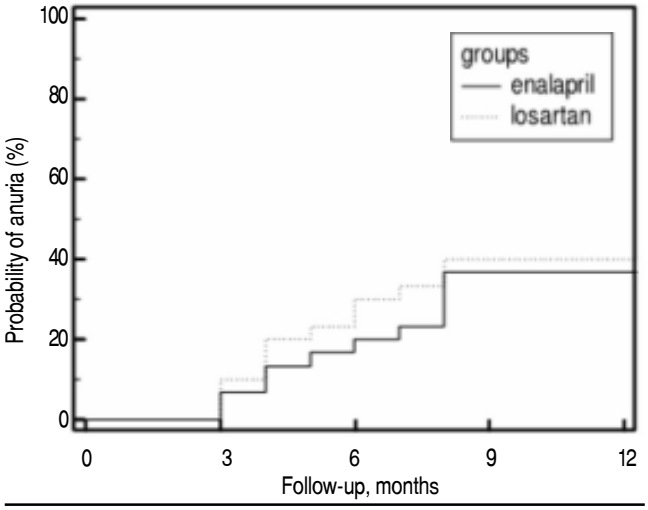


Figure 1. Residual glomerular filtration rate at baseline and during follow-up in the two groups. Error bars = 95% confidence interval.



Number at risk				
Group: Enalapril				
30	28	24	19	19
Group: Losartan				
30	27	21	18	18

Figure 2. Kaplan Meier estimation of patients who progressed to anuria in the two groups.

Table 2. Comparison of residual renal function among the groups.

	HCG (n = 30)	Enalapril group (n = 30)	Losartan group (n = 30)
Baseline RRF (mL/min/1.73 m^2)	3.68 ± 0.48*	3.65 ± 1.6	4.1 ± 2.01
12 months RRF (mL/min/1.73 m^2)	1.4 ± 0.29	2.36 ± 0.38**	2.54 ± 0.47**

HCG: historical control group. *$p > 0.05$ *vs.* baseline enalapril and losartan groups. **$p < 0.05$ *vs.* HCG at 12 months.

Table 3. Adverse events.

Parameter	Enalapril group (n = 30)	Losartan group (n = 30)	p
Episodes of peritonitis (n)	6	7	NS
Cardiovascular events (n)			
Fatal	0	0	NS
Nonfatal	3	4	
Hospitalization, patients admitted (n)	5	4	NS
Cough (n)	2	3	NS
Hyperkalemia (n)	0	0	NS

in the enalapril group and 1.3 ± 0.3 g/24 h in the losartan group (ns), and at the end of the study 0.400 ± 0.100 g/24 h in the enalapril group and 0.500 ± 0.100 g/24 h in the losartan group (ns).

There were not differences in number of hospitalizations between the groups. The frequency of infections and peritonitis was low and similar in the two groups. There was good drug tolerance in both groups, the frequency of cough was minimal, and there were not hyperkalemia episodes (Table 3).

DISCUSSION

There are two RCT's showing the benefit of ACEi/ARBs on RRF preservation in PD patients.[15,16] The time course of RRF declination was similar in both studies. In one of them, ramipril use over 12 months was associated to a significant average RRF declination of 2.07 ml/min per 1.73 m^2 *vs.* 3.0 mL/min per 1.73 m^2 in the control group. The difference between the average changes in RRF from baseline to 12 months was 0.93 mL/min per 1.73 m^2 (95% CI, 0.09 to 1.78 mL/min per 1.73 m^2) between ramipril and control group.[15] The other study showed that valsartan significantly slowed the progressive decline of RRF (4.3 ± 0.7 to 3.2 ± 0.3 mL/min/1.73 m^2) in 34 Japanese CAPD patients, as compared to controls (5.9 ± 0.5 to 2.8 ± 0.4 mL/min/1.73 m^2).[16] However, other recently published observational cohort study, could not confirm the results of the two aforementioned studies showing no differences between the cohort receiving ACEi or ARBs treatment and the control group in the decline of RRF at two and three years of follow-up.[18] Some limitations of this work are that it is an observational study, the information about treatment with ACEi/ARBs before the start of dialysis was not available, and it is unknown why the patients were prescribed ACEi or ARBs.

The aim of the present study was to compare the effect of two good pharmacologic alternatives for RRF preservation in APD patients: an ACEi (enalapril) and an ARBs (losartan). We decided to compare these two very effective treatments because enalapril is the first choice for this purpose in Mexico and losartan represents another treatment option.

The mean of age of the patients included in the present study is 45 years, they are younger than the average patients on PD in developed countries, but of similar age than patients from other published Mexican cohorts.[19,20] In 43% of the patients the cause of CKD was diabetic nephropathy.

There is not a control group without treatment, because by the time the study was approved and initiated it was widely accepted in the medical literature that ACEi and ARBs are effective for RRF preservation,[15,16,28] and that preserving RRF in PD patients is very important,[17] so it was considered unethical to leave a group of patients without the benefits of the treatment. However, we included a HCG to assess the natural history of RRF decline without treatment in a group with features similar to those of the enalapril and losartan groups.

Baseline RRF in the HCG was similar to baseline RRF in both treated groups, but RRF at 12 months in the HCG was significantly lower than RRF at 12 months in both treated groups. This result suggests that treatment with enalapril or losartan is useful to preserve RRF in patients in APD.

Using a HCG is a limitation of the study. The patients in the HCG had similar age, gender, and time in APD, and they were treated at the same healthcare facility than the enalapril and losartan groups. However, the group was non-randomized, non-concurrent, non-parallel and non-synchronic, so this conclusion should be taken with caution.

Proteinuria was similar in the two groups at the beginning and at the end of the study. The urine output

declined progressively during the study in both groups and there were similar proportions of patients with anuria in both groups at the end of the study.

The possible benefits of enalapril and losartan in RRF preservation, seem to be related to inhibition of the actions of AII and TGFβ on the remaining functional glomeruli, maybe avoiding progressive glomerulosclerosis, and extracellular matrix accumulation, independently of blood pressure control.[21,22] At the beginning of the study blood pressure was normal, and during the follow-up period it was maintained within the pre-specified target values in both groups.

The study includes only patients on APD. There are no reported differences between CAPD and APD patients regarding RRF declination rate.[23-27] APD has become more popular over the last years, the global trend is to use APD more frequently than CAPD, and maybe in a few years APD will be the predominant PD modality used all over the world.

The main weaknesses of the study are the small population, the lack of blindness and the use of a HCG. Its strength is that it is a parallel randomized controlled trial. Its originality lies in the comparison of an ACE inhibitor and an ARB that has not been previously done, and that it was carried out in a population of patients receiving APD.

We did not demonstrate differences between enalapril and losartan in slowing RRF decline in patients on APD. Any of them may be a suitable alternative for RRF preservation in young APD patients. The demonstration of equivalence of enalapril and losartan for RRF preservation may be important because the cost of the two alternatives is different. This may be especially relevant when there are economic constrictions. On the other hand, disregarding costs considerations, the knowledge that any of the two alternatives may be useful for RRF preservation is important in cases of intolerance to one of the drugs.

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