

Efficacy of pentoxifylline for reduction of proteinuria in type II diabetic patients

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Abstract

Background: Diabetic nephropathy is considered to be the most common cause of end stage renal disease (ESRD). Proteinuria is declared as the most marked risk factor in progression towards ESRD. The aim of this study was to evaluate the efficacy of pentoxifylline for reduction of proteinuria in type II diabetic patients.

Methods: From May 2007 to June 2008, this randomized clinical trial study was performed on 60 type II diabetic patients with proteinuria over 500 mg/day despite receiving angiotensin receptor or angiotensin converting enzyme inhibitors. These patients were randomly divided into group A (Placebo) and group B (Pentoxifylline 400 mg 3 times daily). A twenty-four hour urine protein and creatinine clearance were assessed before and after three months of treatment.

Results: Among the 56 patients, 38 were females and 18 were males. The mean age of patients in the placebo group was 57.6±9.3 and in the treatment group was 55.3±9.3 years. The duration of the disease in the placebo group was 14.03±5.7 and in the treated group was 11.9±6.2 years. The reduction of proteinuria in placebo group was 294±497 mg/dl and in the case group was 979±695 mg/dl (p<0.05). The mean creatinine clearance in placebo group was 79.4±19.9 and in the case group was 80.6± 22.8 mL/min (p>0.05).

Conclusion: The results show that adding pentoxifylline to other approved angiotensin system inhibitors can significantly reduce proteinuria in diabetic nephropathy and influence progression of the disease with no effect on renal function.

Key words: Pentoxifylline, Proteinuria, Type II Diabetes, Nephropathy.

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Diabetes mellitus is a group of common metabolic disorders characterized by hyperglycemia. With the increase of the worldwide prevalence of diabetes, it still remains one of the most common causes of morbidity and mortality in the world. Although the prevalence of both types of diabetes is increasing worldwide, it has been expected that type 2 diabetes mellitus (T2DM) rises more significantly in the future with regard to population obesity and inadequate physical activity (1).

The most important diabetic complications include retinopathy, neuropathy and nephropathy. Diabetic nephropathy is considered to be the most common cause of end stage renal disease (ESRD). In recent years, our knowledge about its complicating processes, the interfering factors in disease progression and treatment options has increased remarkably to improve renal function and postpone related lesions. However, the increasing population of these patients imposes high costs including dialysis, drug treatments and kidney transplantation to governments (2). Because the long term dialysis is the main cost (resource), preserving patients in pre- ESRD stages seems to be the most logical way to reduce the associated costs and the patients' suffering and also to postpone dialysis or kidney transplantation (2). Albuminuria or proteinuria is an independent risk factor demonstrating progression of renal disease (3).

In large studies done on great numbers of diabetic patients, urinary protein excretion rate was declared as the most marked risk factor in progression towards end stage renal disease (4). Such increased risk justifies the need to reduce proteinuria in these patients (5).

Although acceptable and appropriate treatment is not completely understood in patients with type II diabetic nephropathy, information about protective effects of angiotensin inhibitors has been reported in these patients (6). Currently ACEIs and ARBs have been used to reduce proteinuria, but the amount of remained proteinuria (albuminuria) after treatment is still considered the main criterion in nephropathy progression (7-9). Therefore, maximum kidney protection can be obtained with least proteinuria (10-11). And almost in all cases, there is a need of more than one treatment to achieve this goal (11).

Recent researches have shown that pentoxifylline (PTX) has the ability to reduce proteinuria in diabetic patients with normal renal function (12, 13). This drug, a methyl xanthine derivative, is a blood flow regulator and a non-selective phosphodiesterase inhibitor which reduces inflammatory factors including TNF- α , IL-1 and IL-6 playing a role in the pathogenesis of renal interstitial fibrosis and progression of diabetic nephropathy (14, 15).

The existing data on human and animal models indicate that there is a strong scientific basis for using pentoxifylline as an anti-proteinuric drug (16). Therefore, it seems that pentoxifylline can preserve renal function with further reduction in proteinuria and subsequently reduces cardiovascular complications and patients' costs and suffering. The aim of this study was to evaluate the efficacy of pentoxifylline for reduction of proteinuria in type II diabetic patients who were unresponsive to angiotensin receptor or angiotensin converting enzyme inhibitors.

Methods

From May 2007 to June 2008, this randomized clinical trial was done on 56 type II diabetic patients with proteinuria over 500 mg/day in spite of receiving angiotensin system inhibitors for at least three months in the Department of Nephrology of Babol University of Medical Sciences. The exclusion criteria included type I diabetic patients, creatinine more than 1.5 mg/dl (creatinine clearance under 60 mL/min) and patients with hemodialysis and non-diabetic glomerulopathy with proteinuria. The inclusion criteria

included type II diabetic patients with proteinuria over 500 mg/day unresponsive to angiotensin system inhibitors for at least three months. The sample size was estimated to be 28 patients in each arm.

The patients were divided through random number tables into two groups; placebo group received angiotensin system inhibitors only and the case group who received angiotensin system inhibitors plus pentoxifylline 400 mg 3 times per day. They received these agents for three months. Pentoxifylline (400 mg, SR) was prepared from Apo Tex Inc, company, Canada with Batch no (L) HM9359. Only the relevant pharmacist was aware of these two groups. For all the patients, a 24-hour urine proteinuria was evaluated based on mg per day before PTX prescription.

The patients were treated and followed up for three months. A week after drug completion, 24-hour urine protein was evaluated in the same laboratory where the patients had been previously tested and the relevant information was recorded. The patients' 24-hour urine and creatinine clearance were calculated using Spach method and Cockcroft-gault formula, respectively. The study was approved by Babol Medical Research Center and the Ethics Committee of Babol University of Medical Sciences. All the patients gave their written consent forms. The study was under the Iranian Registration for Clinical Trial (Registration ID number: IRCT 201010144941N1).

All the patients filled out the written consent forms after being given information about the drug. The data were analyzed using SPSS15. Parametric analysis t-test, paired t-test and Chi-square test were used when appropriate. To adjust the variances and to perform statistical tests, we used the logarithms of proteinuria levels.

Results

Among the 56 patients, 38 cases were females. The mean age of patients in the placebo group was 57.6 ± 9.3 and in the treatment group was 55.3 ± 9.3 years ($p > 0.05$). The duration of the disease in the placebo group was 14.03 ± 5.7 and in treated group was 11.9 ± 6.2 years ($p > 0.059$). The twenty four hour urinary proteinuria before the beginning of the study and one week after study completion in both groups are shown in figure 1.

There was a significant reduction of proteinuria before and after treatment in both groups ($p = 0.004$ and $p = 0.001$, respectively) (table 1). The mean reduction of proteinuria in

the case group was higher than the placebo group ($p < 0.001$) (table 1). (61.44% reduction in pentoxifylline compared to 19.65% in placebo group). Comparing creatinine clearance rates before and after treatment showed no significant

differences between the two groups (table 1). In addition, diabetes duration as well as age and sex distribution represented no significant differences between the two groups.

Table 1. The mean (\pm SD) distribution of protein excretion and creatinine clearance in placebo and pentoxifylline groups before and after treatment

Groups (n=28)	Reduction of Proteinuria(mg/d) (before & after treatment)	CrCL(ml/min) Before treatment	CrCL(ml/min) After treatment
Placebo	-294.14 \pm 497.43	80.9 \pm 19.92	79.36 \pm 19.92
Treated	-979.25 \pm 695.44	80.18 \pm 24.80	80.62 \pm 22.84
Pvalue	0.001	0.8	0.7

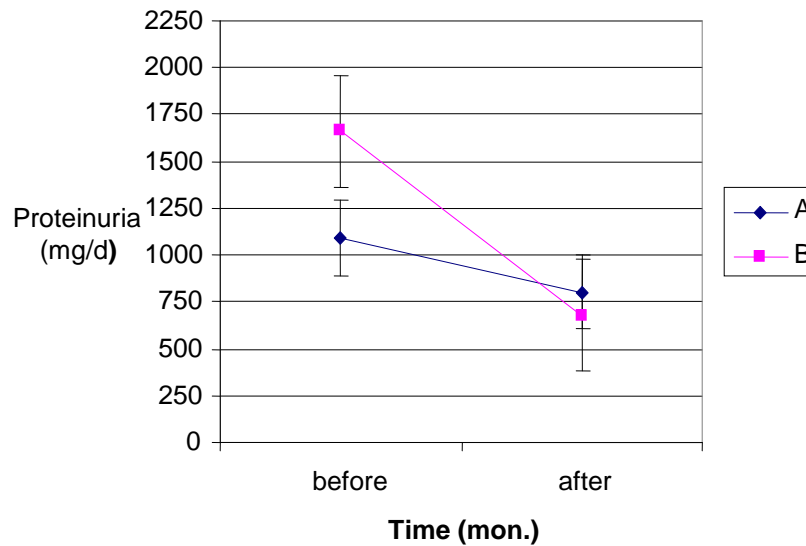


Figure 1. Distribution of proteinuria before and after the drug use in group A (Placebo) and group B (Pentoxifylline)

Discussion

Reducing the amount of urinary protein excretion rate can delay renal disease progression. To date, renin-angiotensin system inhibitors have been widely used to achieve this goal. Nevertheless, there are still patients with obvious proteinuria and progression towards end stages of the disease in spite of using these drugs. In addition, these medications are not feasible in many patients due to complications such as hyperkalemia or angioedema. Therefore, the efforts for finding other effective drugs to reduce proteinuria or to increase the effectiveness of existing drugs or as a substitute seem to be rational. Recent researches have indicated the ability of pentoxifylline in reducing proteinuria in diabetic patients with normal kidney

function (12, 13). In this regard, the impact of pentoxifylline was examined in type II diabetic patients with proteinuria over 500 mg/day in spite of being under angiotensin receptor or angiotensin converting enzyme inhibitor treatment. In this study, we found that pentoxifylline (PTX) can significantly reduce protein excretion in patients with noticeable proteinuria despite of taking renin-angiotensin system inhibitors and is in accordance with the results of other studies in this area (17, 18).

Among these studies, few researches compared the effect of PTX with captopril in reducing proteinuria; PTX has decreased proteinuria to the same extent as captopril (18). During the 12-month period study on 85 type II

diabetic patients with proteinuria and renal failure, it has been found that PTX can dramatically lessen proteinuria in patients with kidney failure (stages 3 to 5) if added to losartan (19). The last two studies have been done after the present research. In addition, the comparison between the effects of captopril and PTX on 40 patients demonstrated the similar effects in reducing proteinuria (20).

The most effective anti-proteinuric impact of PTX is the drug's ability to regulate the production of inhibitory proteins and inflammatory cytokines. Diabetic nephropathy is a primary inflammatory process and existing pieces of evidence show the strong role of inflammatory cytokines like TNF- α in increasing glomerular permeability to albumin. Proteinuria can also trigger severe inflammation by inducing secretion of inflammatory mediators from renal tubular cells.

In this study, we demonstrated the daily use of 1200 mg PTX in a 3-month period besides angiotensin system inhibitors that can reduce proteinuria far more than the placebo group who only received angiotensin system inhibitors. Fortunately, no adverse effects or intolerance to drug were found during the period of treatment.

Another point is, there was no need to change the dose of angiotensin inhibitors (ACEI or ARBs) during the three-month study; therefore, the drug dose-dependent efficacy in proteinuria reduction did not influence the final results. It has been shown that maximal doses of ACEI or ARB may make a refractoriness to effects of PTX (21), but in our study, the drug doses were moderate and it did not seem to be the case. The weakness of this study was the measurement of urine total protein instead of albumin. This measurement is popular in the developing countries. Another weakness is the non-matching in the mean of proteinuria of both groups that may influence the outcome of the study. However, statistically more significant reduction of proteinuria in case group covers this weakness. Another limitation of this study was the lack of facilities for the detection of TNF- α in the urine. In summary, the results show that adding PTX to other approved angiotensin system inhibitors can reduce proteinuria significantly in diabetic nephropathy and influence progression of the disease.

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