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Efficacy of Losartan in Treatment of Hyperuricemia in renal transplant recipients

Sima Abedi Azar*

Department of Nephrology, Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
Corresponding author

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A B S T R A C T

Hyperuricemia is one of complications after renal transplantation (RTX) and it is predictor and risk factors for cardiovascular events. Losartan decreases serum uric acid concentrations by reducing proximal tubular reabsorption of uric acid, and it can be a useful agent for treatment of hyperuricemia. We aimed to evaluate the effect of Losartan on serum uric acid concentrations in patients whom receive immunosuppressive drugs which interfere with uric acid lowering agents after kidney transplantation. Seventy renal transplant recipients(RTRs) (men=45, F=25) mean age=41.94±0.72 years, with stable graft function with serum creatinine (SCr) concentration less than 1.5 mg/dl and Hemoglobin(Hb) concentration greater than 110 g/L were enrolled in the study. The patients were divided into 2 groups (Losartan group, n = 35; and control group, n = 35), Patients in the Losartan group received Losartan, 50 mg/d; patients in the control group did not receive Losartan. Each patient was evaluated at base line and followed up for 6 months at 1, 2, 3, and 6 months after entrance the study by physical examination; laboratory evaluation for Hb, serum uric acid, SCr, urea nitrogen, albumin, and potassium concentrations; and whole-blood cyclosporine(CsA) trough level, 24 hours urine cr and uric acid. All patients received triple immunosuppressant therapy including CsA, azathioprine, and prednisone. 2 patients in the Losartan group and 1 patient in the control group dropped out because of anemia and noncompliance respectively. At baseline, mean concentrations were similar between the Losartan and control groups for serum uric acid. The serum uric acid concentration in the Losartan group after 6 month decreased from7.60±0.4 to 6.85±0.31 (P <0.0001) compared with baseline, and compared with controls (P < 0.001). 24 hours uric acid significantly increased from 319.23±67.62 to 370.20±73.1 at month 6(P <0.0001).The Hb level in the Losartan group decreased at months 3, and 6 compared with controls and baseline, but it was not statically significant. There was no significant decline in glomerular filtration rate in the Losartan group. Losartan can use for treatment of hyperuricemia in RTRs without significant side effects

Introduction

Hyperuricemia is common after renal transplantation (RTX) (1) and it has been reported in 5-84% (2) of transplanted patients. It is recognized as an independent risk factor for cardiovascular disease and it induces the vascular modeling and carotid

intima-media thickness (3). Although uric acid is an antioxidant (4) but by increasing platelet activation and pro thrombotic effect and then inducing inflammatory pathways leads to smooth muscle proliferation and sensitizing smooth muscle cells and ends to tissue ischemia (5) and endothelial damage and premature atherosclerosis(4). Hyper uricaemia is common in RTRs, some reports up to84%(6) and because of additional side effect of cyclosporine A(2)which decreases the glomerular filtration or impairs tubular secretion of uric acid (7), long term urate lowering agents is required. In this regard Allopurinol because of its interaction with azathioprine and induction of sever bone marrow suppression should be used with caution and with close renal function monitoring. It's been reported some agents like fenofibrate, atorvastatin, amlodipine, Losartan have additional benefit of lowering serum urate(2). Losartan besides of its antihypertensive and renal protection effect(1),reduces proteinuria and interstitial fibrosis, and by lowering tubular reabsorption of uric acid it can increase excretion of uric acid (4, 8)and in some studies could be able lower uric acid in8% and in 17% uricosuria(1). Because of side effects of hyperurecemia and difficulty of its treatment in RTXs whom receive Azathioprine, we aimed to evaluate the efficacy of losartan on hyper urecemia and hyperuricosuria of RTXs.

Patients and methods

Seventy renal transplanted patients (F=25, M=45) whom underwent living kidney donation at least 6 months before entering the study with uric acid more than 7 mg/dl enrolled in study. All of patients had stable kidney function (serum creatinine <1.6) and serum Hgb >11.5 mg/dl. Patients with transplanted kidneys artery stenosis, recently acute rejection, acute cerebrovascular events, use of Angiotensin converting enzyme inhibitors or angiotensin receptor blockers, use of urate lowering agents in previous months excluded from the study and during the study the patients whom became anemic or systolic blood pressure dropped below 100 mmHg were omitted from the study. Patients were divided in two groups; half of them received Losartan 50 mg twice daily. Each patient was evaluated at base line and followed up for 6 months at 1, 2, 3, and 6 months after entrance the study by physical examination; laboratory evaluation for Hb, serum uric acid, SCr, urea nitrogen, albumin, and potassium concentrations; and whole-blood CsA trough level, 24 hours cr and uric acid. Also blood pressure, demographic data, transplantation duration and renal failure causes were recorded. All of patients were received cyclosporine, Azathioprine and steroids as immunosuppressive agents, and none of them received ACEIs, diuretics, Amlodipine, fenofibrate and statins and urate lowering agents.

Result and Discussion

The mean age of patients was 41.94±0.72 years (39.7±11.2 years in Losartan group and 43.9±10.3 in control group), without significant difference between them. 2 patients in the Losartan group and 1 patient in the control group dropped out because of anemia and noncompliance respectively. Mean transplantation duration was 43±19.9 months in Losartan and 46±27.4 months in control group without any significant differences $p<0.63$.The mean Scr in Losartan group at base line was 1.32±0.4 mg/dl and in control group 1.47±.5 mg/dl without significant deference between them $p<0.2$. After 6 months the S cr level significantly raised to 1.44±0.4 ($p<0.003$) in Losartan group but such increment was not found in controls. About serum potassium,

there was not significant deference in two groups in base line and Losartan consumption didn't affect potassium level after 6 months. Mean serum uric acid decreased significantly from 7.6±0.4 to 6.85 ±0.3 (P<0.0001) after 6 months but in control group this change was not significant compared with baseline (7.4±0.12 versus 7.23±11), and compared with controls (P < 0.001). 24 hours uric acid significantly increased from 319.23±67.62 to 370.20±73.1 at month 6 (P <0.0003) in Losartan group but in control group the increment was not meaningful (326.5±79 to 326.6±82.2, p<0.28). Mean arterial pressure dropped significantly from 86.2±3.7 to 81.9±3 in Losartan group (P<0.0001) 6 months after drug consumption. The Hb level in the Losartan group decreased at months 3, and 6 compared with controls and baseline, one patient dropped out because of Hb<10, but in remained it was not statically significant.

As we mentioned hyperurecemia which more induces with cyclosporine consumption in RTRS can affect patient and graft survival and as a independent cardiovascular risk factor can leads to serious cardiovascular events(1)and cause urate nephropathy and uric acid stones(9), so its treatment is mandatory but is challenging in patients whom use azathioprine as immunosuppressive drugs. Rezai at al showed that hyperurecemia can occur in 10.5 % of RTRs about 4 years after RTX (10) and in Schmidt As study it has been reported up to 84%, we enrolled the hyperurecemic patients to our study that received azathioprine as immunosuppressive treatment because of its treatment difficulty, so we didn't estimate the incident of hyperurecemia. Losartan by lowering tubular reabsorption of uric acid can increase of uric acid excretion, kamper et al showed that use of 50 mg Losartan by transplanted patients can increase 17% in uric acid excretion and 8% uric acid reduction (4) Our findings demonstrate that in kidney transplant recipients, Losartan therapy significantly decreases the serum uric (10% uric acid reduction and 16% increase in uric acid excretion).

In our study mean arterial pressure dropped significantly from 86.2±3.7 to 81.9±3 in Losartan group, which is expectable and Schmidt As in his study confirmed anti-hypertensive effect of Losartan besides its uricosuric effect. Hyperkalemia is another complication of ARBs. In our study the Losartan effect on serum K level was not so significant like previous studies (6).

It has been reported in some studies (11) that Losartan by its effect on bone marrow can prevent post-transplant erythrocytosis (PTE)which increases the morbidity of cardiovascular diseases, However as an side effect the anemia caused by ARB therapy in patients without PTE has been reported about 42.8%(12) of patients that Hb was not so high. The Hb level in our patients was reduced but it was not statically significant may be it needs more patients for right judgment. about increased SCr or decreased GFR which restricts the use of ARBs in transplanted patients it confirmed in systematic reviews that a significant decrease in GFR occurs(13) In present study, SCr concentration in 3 month in the Losartan group was increased but it remained stable after 3 months without any needs to stop the drug.

Conclusion

Losartan has a significant effect in reducing of hyperurecemia and increasing urinary excretion of uric acid in patient with renal transplantation and can use for treatment of hyperuricemia in RTRs without significant side effects.

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