Original Article

Allopurinol Effects on Residual Renal Function in End-Stage Renal Disease Patients Undergoing Peritoneal Dialysis: Randomized Controlled Trial

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ABSTRACT

Objective: There is increasing evidence to show that hyperuricemia may have a pathogenic role in the progression of renal diseases. We performed a prospective, randomized, controlled trial to investigate the renal effects of allopurinol treatment in hyperuricemic patients with end-stage renal disease (ESRD) who undergo peritoneal dialysis. **Methods:** This was a unicenter, randomized, controlled clinical trial conducted in "Alzahra Hospital, Isfahan, Iran." Patients were randomly assigned into treatment or control group. Treatment-group patients were administered a starting allopurinol dose of 100 mg/day. The dose was adjusted according to serum uric acid level, aiming to maintain uric acid levels within the normal range. Participants were followed up for 6 months after receiving the medicine. Residual renal function (RRF) was assessed by measuring the renal component of Kt/V urea and estimating the patient's glomerular filtration rate (GFR) by calculating the mean of urea and creatinine clearance. In addition, systolic and diastolic blood pressure and serum level of creatinine were measured every 3 months during the follow-up period. **Findings:** Eighty patients were enrolled in the study and divided into two groups, including 40 ESRD patients receiving allopurinol and 40 ESRD did not receive allopurinol and considered as the control group. GFR measurements showed that there was not a significant difference between patients' RRF of two groups. However, allopurinol group had higher RRF than the control group during the follow-up period. Evaluating RRF by Kt/V showed the same results. **Conclusion:** Our study demonstrated significant effects of allopurinol on decreasing serum levels of uric acid in ESRD patients undergoing peritoneal dialysis. On the other hand, renal residual function of patients under treatment with allopurinol was better than the control group. We recommend that further studies should be conducted on the effects of allopurinol with greater sample size and longer time of follow-up.

KEYWORDS: *Allopurinol, end-stage renal disease, peritoneal dialysis, residual renal function*

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INTRODUCTION

Patients with end-stage renal disease (ESRD) may suffer from hyperuricemia and expressively its early prevention rather works on their favor.[1] There is also increasing evidence to indicate the hyperuricemia pathogenic role in the progression of renal diseases, instead of merely reflecting decreased renal uric acid excretion. Hyperuricemia is a crucial cause in the progression of kidneys to chronic and progressive renal diseases, systemic hypertension, proteinuria, renal dysfunction, and chronic kidney disease (CKD) which should be considered as its adverse effects.[2] In patients

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with CKD who perform peritoneal dialysis, higher uric acid levels raise the mortality. In addition, an independent representative for the death of all patients is not out of mind. The presence of some other disorders, for instance, diabetes or malnutrition may cause mortality in these patients with lower levels of uric acid.[2,3]

Few surveys have been conducted on patients with chronic renal disease undergoing peritoneal dialysis. Previous studies have shown that hyperuricemia can disrupt endothelial function and cause rapid renal impairment. Hyperuricemia makes dialysis ineffective and ultimately leads to inappropriate outcomes in these patients.[3] An elevated uric acid level reported as a risk factor in ESRD female patients with immunoglobulin A (IgA) nephropathy.[2] Therefore, uric acid might be a treatable target in female IgA nephropathy patients. An elevated uric acid level is also correlated with the development of renal insufficiency in either patient with type 2 diabetes or individuals with normal kidney function.[3]

Allopurinol is known as an inhibitor of xanthine oxidase enzyme. Conditions such as gout that is exerted by increased uric acid serum level are treated by this support since the past few decades.

More recent data show that xanthine oxidase also plays an important role in variety types of ischemic and alternative types of vascular and tissue injuries, inflammatory diseases, and CKD.[4] Allopurinol decreases serum uric acid level by inhibiting xanthine oxidase enzyme. In experimental rat models, hyperuricemia-induced functional and structural injury of the kidney were prevented by allopurinol treatment, which maintained serum uric acid levels in the normal range.[5] Therefore, ways to manage and reduce serum uric acid level may have a beneficial effect on improving kidney function or slowing the progression of renal diseases in clinical practice. We, therefore, performed a prospective, randomized, controlled trial to investigate the renal effects of allopurinol treatment in hyperuricemic patients with ESRD who undergo peritoneal dialysis.

Methods

This was a unicenter, randomized, controlled clinical trial. ESRD patients with hyperuricemia who were under peritoneal dialysis were enrolled in the study. The present study conducted in "Alzahra Hospital, Isfahan, Iran," from December 2016 to 2017.

Our study was approved in the "Isfahan University of Medical Sciences Ethics Committees, Isfahan, Iran (approval code IR.MUI.REC.1395.3.837)." Furthermore, the present study approved by the Iranian Registry of Clinical Trials (Approval code: IRCT20090905002417N20). Written consent form of all the patients was obtained before the enrollment.

Patients were randomly assigned according to a computer-generated list into either the treatment or control group. Included participants had to fulfill the following inclusion criteria: (1) 18–80 years old patients, (2) undergoing peritoneal dialysis at least for 3 months, (3) with hyperuricemia (uric acid ≥7 mg/dl in male and uric acid ≥6 mg/dl in female), (4) glomerular filtration rate (GFR) had to be at least 2cc/min/m^2, and (5) patients who filled the written consent form. We excluded the following patients who had: (1) allergy to allopurinol or major reactions including Steven–Johnson syndrome, (2) changing peritoneal dialysis to hemodialysis, (3) kidney transplantation, (4) took nephrotoxic drugs, and (5) death. After enrollment, patients were randomly divided into two groups: allopurinol group (receiving allopurinol) and control group (without receiving allopurinol). Patients' medicines, including antihypertensive drugs, continued during the study [Figures 1 and 2].

Treatment-group patients were administered a starting allopurinol dose of 100 mg/day (made by Jalinous pharmaceutical company, Tehran, Iran). The dose was adjusted according to serum uric acid level, aiming to maintain uric acid levels within the normal range. Dosages of antihypertensive drugs, lipid-lowering agents, and steroid or cytotoxic drugs were continued and adjusted according to the individual patients' clinical conditions. Furthermore, any changes in drug dosages or intervals were recorded. Any adverse event considered to be related to the use of allopurinol was recorded during the follow-up assessment. For minor adverse events such as skin rash, vomiting, pruritus, and nausea, allopurinol withheld temporarily until symptoms resolved; allopurinol therapy then restarted and the patient closely monitored. The medication would discontinued if adverse effects recurred. For serious adverse events, including Stevens–Johnson syndrome and hepatitis, allopurinol therapy would be discontinued at once and the study would be terminated. To do blood measurements, 5 cc of peripheral blood sample was taken from all of the patients. Blood samples were drawn into standard serum tubes, allowed to clot, separated by centrifugation, and stored at −20°C until they were studied. Serum level of uric acid in patients and controls was measured by the Hitachi analyzer (manufactured by Japan) in the Alzahra Hospital laboratory.

All cases that fulfilled inclusion criteria were screened for fasting serum uric acid level. Baseline characteristics

of all patients, including their age, sex, and history of diabetes mellitus, were registered. Furthermore, blood urea nitrogen, blood and urine creatinine level, and serum level of uric acid were measured. Moreover, solution and number of peritoneal dialysis sessions were recorded. Participants were followed up for 6 months after receiving medicine. During every month of follow-up, systolic (SBP) and diastolic blood pressure (DBP) were recorded. In addition, serum level of creatinine (cr) and uric acid was measured at months 0, 1, 3, and 6. Residual renal function (RRF), which can provide a significant component of total solute and water removal, assessed by measuring the renal component of Kt/V urea and estimating the patient's GFR by calculating the mean of urea and creatinine clearance. Adverse events related to allopurinol medication were recorded in each visit.

All statistical analyses were conducted using the IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA). Categorical data were compared using the repeated measurement test and continuous variables using the *t*-test. Comparison of many parameters between different intervals and baseline was performed using the paired Student's *t*-test. Analysis of variance test was used when parameters of more than two groups were compared. Statistical significance defined as $P < 0.05$.

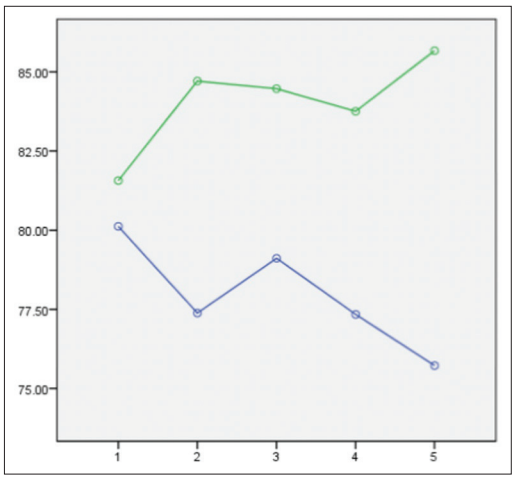

Figure 1: Mean diastolic blood pressure of patients (mmHg)

Results

Eighty patients were enrolled in the study and divided into two groups [Figure 3]. Detailed demographic data of two groups are demonstrated in Table 1. There was not a significant relationship between renal residual function and demographic features of patients including their age and sex.

None of the patients in both groups had preexisting gout. There was not a significant difference between mean serum levels of uric acid between two groups at baseline. While there was not a significant difference between mean serum levels of uric acid after 1 month, it was significantly decreased after 3 and 6 months of follow-up [Table 2].

SBP and DBP measured every 1 month after beginning the study. Table 3 demonstrated these measurements. There was not a significant difference of mean level of SBP and DBP between two groups after 3 months of follow-up. However, by the 5th month of follow-up, mean SBP and DBP of patients in the allopurinol group decreased significantly, and it remained till the end of the study [Figures 1 and 4].

As said before, renal residual function evaluated by two methods, including measurement of Kt/V and GFR. As demonstrated in Table 4, GFR measurements showed that there was not a significant difference between patients' RRF of two groups ($P > 0.05$). However, allopurinol group had higher RRF than the control group during the follow-up period. Evaluating RRF by Kt/V showed the same result. There was not a significant difference between RRF of two groups [Figure 5]. Although RRF of patients who received allopurinol had an ascending trend [Table 4] in both groups, there was no significant

Table 1: Baseline characteristics of patients in two study groups

Patients' characteristics	Allopurinol group (*n*=40), *n* (%)	Control group (*n*=40), *n* (%)
Female/male	18 (45)/22 (55)	20 (50)/20 (50)
Age (years)	59.1±16.4	53.8±16.8
Diabetes mellitus		
Yes	24 (60)	20 (50)
No	16 (40)	20 (50)
Number of peritoneal dialysis sessions per day		
One	6 (15)	5 (12.5)
Two	13 (32.5)	15 (37.5)
Three	18 (45)	18 (45)
Four	3 (7.5)	2 (5)

Data presented as mean±SD, or *n* (%) of patients. SD=Standard deviation

association between renal residual function and the number of performed dialyses ($P > 0.05$). In addition, there was not any association between solution of peritoneal dialysis and renal residual function of patients in both groups.

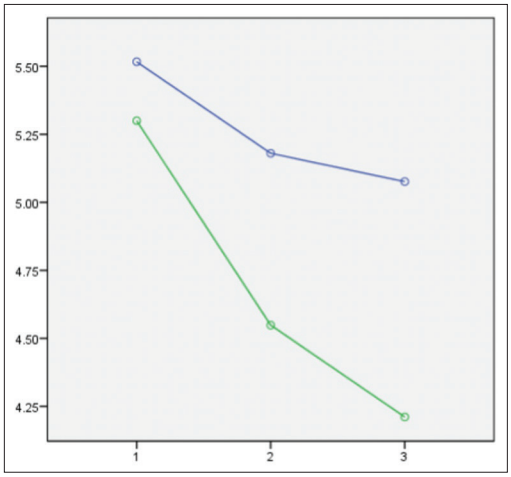

Figure 2: Residual renal function by glomerular filtration rate measurement

Table 2: Mean serum level of uric acid (mg/dl) in different phases of the study

Study period	Allopurinol group	Control group	*P**
Before the intervention	8.1±1.0	7.7±1.1	0.6
After 1 month	7.9±1.1	7.1±0.9	0.16
After 3 months	6.4±1.1	7.1±0.9	0.001
After 6 months	5.6±1.0	7.7±1.1	0.001

*Paired *t*-test analysis. Data presented as mean±SD. SD=Standard deviation

Discussion

Many recent studies have shown that the higher level of serum uric acid is associated with higher mortality rates in patients with ESRD who are under peritoneal dialysis. Hyperuricemia is an important risk factor for the progression of ESRD. Some recent studies have shown that lowering serum uric acid levels by allopurinol in hyperuricemia patients with CKD may reduce the risk of CKD progression.[6,7] Increasing production or decreasing excretion of uric acid can cause hyperuricemia. In patients with ESRD, urinary uric acid excretion is decreased and lead to hyperuricemia. However, it also depends on the ability of the gastrointestinal system to excrete uric acid.[8]

In our study, while there was not a significant difference between mean serum levels of uric acid after 1 month, it was significantly decreased after 3 and 6 months of follow-up. Su *et al*. did a systematic review in 2017 on 1211 CKD patients with 146 kidney failure events such as ESRD and so on. They revealed that uric acid-lowering therapy, such as allopurinol seemed to improve kidney outcomes in patients who were under treatment for at least 6 months.[9] A cohort study in Japan from 1993 to 2004 on 48,177 screeners (22,949 men and 25,228 women) showed that increased levels of uric acid may lead to more kidney diseases in the final stage. The exact mechanism is not known, but it is probably related to multiple factors such as uric acid nephropathy, arteriopathy, and hypertension.[10]

Hyperuricemia can cause high blood pressure. By the 5th month of our investigation, the mean SBP and DBP

Table 3: Systolic and diastolic blood pressure (mmHg) of patients during the follow-up period

Follow-up period	Mean systolic blood pressure		*P*	Mean diastolic blood pressure		*P**
	Allopurinol group	Control group		Allopurinol group	Control group	
After 1 month	147.8±21.3	129.1±18.0	0.5	77.1±10.9	84.2±17.3	0.7
After 2 months	81.6±9.8	80.0±11.1	0.3	78.1±8.7	82.6±11.3	0.5
After 3 months	138.7±19.1	142.8±23.2	0.5	80.3±8.5	82.8±18.1	0.2
After 4 months	132.7±18.6	141.0±21.3	0.07	79.2±14.6	82.7±12.5	0.3
After 5 months	127.6±16.9	142.5±22.8	0.001	81.6±9.8	80.0±11.0	0.001
After 6 months	121.3±16.7	150.1±27.1	0.001	85.5±13.2	78.5±12.2	0.001

*Repeated-measure analysis

Table 4: Residual renal function of patients assessed by glomerular filtration rate

Follow-up period	Residual renal function assessed by GFR		*P*	Residual renal function assessed by Kt/V		*P**
	Allopurinol group	Control group		Allopurinol group	Control group	
Before the intervention	5.58±2.9	5.50±3.9	0.92	1.8±0.49	2.30±0.68	<0.001
After 1 month	5.55±3.2	5.20±3.6	0.71	1.92±0.63	2.26±0.61	0.019
After 3 months	5.21±2.9	4.51±3.2	0.32	1.95±0.33	2.31±1.46	0.135
After 6 months	5.10±2.8	4.46±3.2	0.2	2.19±0.48	2.1±0.60	0.384

*Independent *t*-test. Data presented as mean±SD. SD=Standard deviation, GFR=Glomerular filtration rate, Kt/V=K (dialyzer clearance of urea), t (dialysis time); V (volume of distribution of urea)

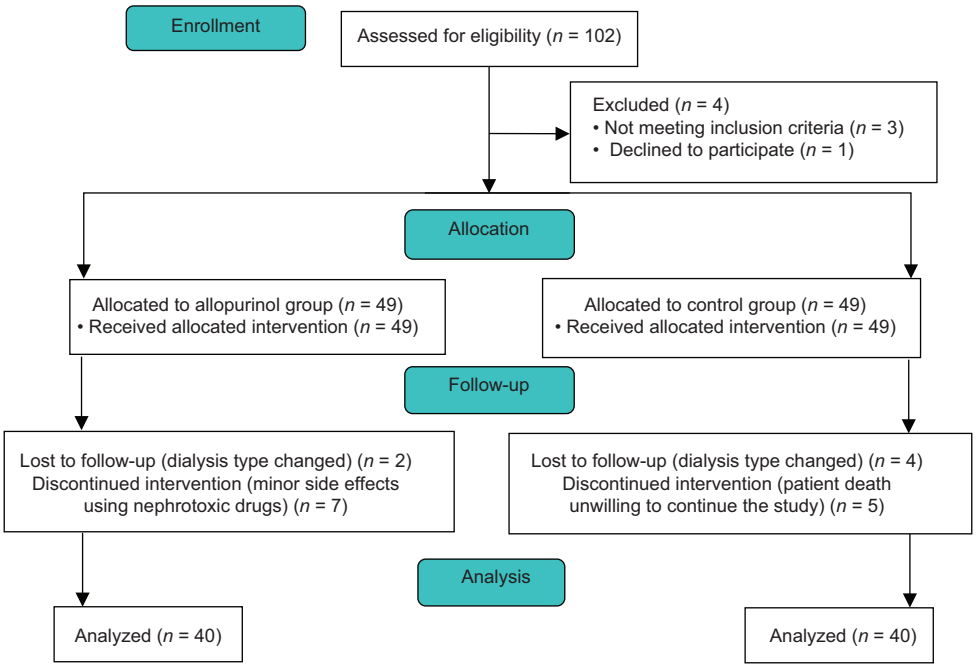

Figure 3: Flow diagram of the study

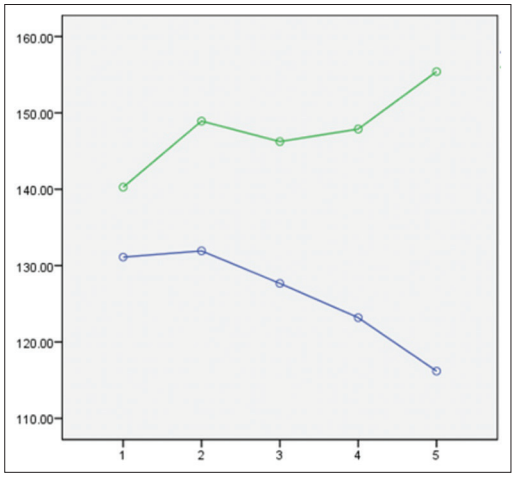

Figure 4: Mean systolic blood pressure of patients (mmHg)

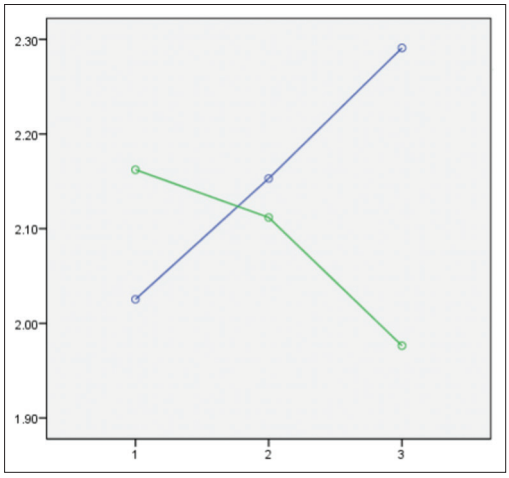

Figure 5: Residual renal function by Kt/V measurement

of patients in allopurinol group decreased significantly and it remained till the end of the study. Mazzali *et al*. studied on rats in 2001 with 3-week follow-up time. They revealed that control of the level of uric acid with allopurinol prevents hypertension and alterations in the level of neuronal nitric oxide synthase and renin.[11] A study of Siu *et al*., in 2006, on 54 hyperuricemic patients that were followed up for 1 year showed that SBP decreased after allopurinol treatment. Blood pressure was not significantly different from the control group who did not receive allopurinol, the reason may be due to the selection of participant. All of their patients had established renal diseases with impaired renal function, and most patients had long time hypertension at the time of hospitalization.[12]

Furthermore, this study revealed that to improve the hypertensive effect of hyperuricemia, it is necessary to start treatment with allopurinol early and once the disease has been established, the effect of decreasing serum uric acid level may be limited.[12]

Unlike the mentioned studies, Kang *et al*., in 2002, found that hyperuricemic rats treated with allopurinol experienced higher proteinuria, higher blood pressure, and higher serum creatinine levels than controls.[13,14] Renal Kt/V (r-Kt/V) is used as an indicator for examining the requirement for dialysis initiation. Clinical trials in peritoneal dialysis indicate that r-Kt/V reduction below the threshold of 2.0/week may indicate an inadequate renal excretion of toxin.[15]

In the present study, we could not show any significant associations between renal residual function and the number of performed dialyses. In addition, there was not any association between solution of peritoneal dialysis and renal residual function of patients in both groups. Unlike our study, in 2008, Marrón *et al*.[16] investigation revealed that peritoneal dialysis compared with conventional hemodialysis associated with a slower decrease in renal residual function. This highlights the usefulness of strategies oriented to preserve both renal residual function and the long-term viability of the peritoneal membrane.[17] In patients with peritoneal dialysis, there are additional techniques that may exacerbate the loss of renal residual function such as peritoneal dialysis prescriptions and modality, bioincompatible dialysis fluid, and over ultrafiltration of fluid that causes dehydration.[17] Uric acid is now recognized to be a mediator of renal disease and progression. Hyperuricemia induces high blood pressure, renal afferent arteriopathy, increased glomerular hydrostatic pressure, and renal scarring. We showed that using allopurinol to decrease serum uric acid levels is safe and may be beneficial in decreasing SBP, DBP, and serum uric acid levels, but this beneficial effect had no relation with the rate of deterioration in renal function.

Studies on using allopurinol in patients with ESRD have been reported different efficacy and safety. Providers should be attentive of the potential risk of hypersensitivity reaction to allopurinol, and they also need to be aware lower initial dose and gradually titration of allopurinol to reach the therapeutic serum level.[18] A study in 2010 on patients with estimated GFR <60 ml/min that were followed up for 24 months showed that allopurinol decreases C-reactive protein and slows down the progression of renal disease in patients with CKD. In addition, allopurinol reduces cardiovascular and hospitalization risk in CKD patients.[19]

A remarkable note about our study results is that these results may be limited due to the concomitant use of antihypertensive drugs in some patients. Another limitation of our study was low number of patients, as well as the short-time follow-up.

Our study demonstrated significant effects of allopurinol on decreasing serum levels of uric acid in ESRD patients undergoing peritoneal dialysis. In addition, SBP and DBP of patients received allopurinol decreased significantly after the 5th month of follow-up. On the other hand, renal residual function of patients under treatment with allopurinol was better than the control group. We recommend that further studies should be conducted on the effects of allopurinol with greater sample size and longer time of follow-up.

Authors' Contribution

All authors contributed to the writing of this article. Firouzeh Moeinzadeh and Mojgan Mortazavi designed the study. Firouzeh Moeinzadeh and Elham Kabiri Naeini contributed to the search of literatures and providing the first draft of the article. Elham Kabiri Naeini performed participant selection, doing study and data gathering. All authors read and approved the article.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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