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The effect of allopurinol treatment regimen on serum uric acid and arterial blood pressure in hemodialysis patients

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Abstract

Introduction: Controlling and reducing serum uric acid levels may have beneficial effects on blood pressure control. The current study was carried out to assess the effects of allopurinol administration on serum uric acid and arterial blood pressure among the patients under hemodialysis.

Methods: This double-blind clinical trial was conducted on 132 hemodialysis patients (two separate groups) suffering from hyperuricemia and hypertension at Imam Reza hospital, Kermanshah in 2014. The first group received a daily dose of 100 mg allopurinol and the second group, as control, received placebo. The demographic data, vital signs, paraclinical data and comorbidities of all patients were recorded in a checklist. Serum uric acid and blood pressure were measured at the end of the first, second and third months. The obtained data were analyzed by SPSS software using t-test, paired t-test and repeated measure t-test.

Results: The results showed that allopurinol significantly reduced systolic and diastolic blood pressure and uric acid level in the patients with chronic renal dysfunction. This reduction was also reported to be significant between the patient and control groups at different times.

Conclusion: Given the beneficial effect of allopurinol on the patients with chronic renal dysfunction, this drug can be used in this group of patients.

Introduction

The hemodialysis patients with chronic renal dysfunction are 10 to 100 times more likely to die than the normal people. This increased rate of mortality is not only due to the common risk factors like obesity, diabetes, high blood fat, smoking and hypertension but also because of specific conditions in this group of patients. Acute complications usually occur during dialysis due to imbalance in cardiovascular system. Some cardiovascular complications include hypotension, ventricular hypertrophy, arrhythmia, cardiac arrest and sudden death (1). In the serum of the patients with renal dysfunction, uric acid is frequently increased as a result of reduced glomerular filtration (GFR) and reduced renal excretion of urate (2).

Uric acid is a weak organic acid with a pKa of 5.75 and is mainly available as monosodium urate (MSU) in physiologic pH (3). On the other hand, uric acid level is normally high in the patients with hypertension and people with the risk of cardiovascular diseases. This increase is observed in 25% of the people with untreated hypertension, 50% of the people consuming diuretics and more than 75% of the patients with malignant hypertension (4). The increased rate of serum uric acid in hypertension may be due to a reduction in renal blood flow. Because low renal blood flow stimulates the reabsorption of urate, it causes hypertension (5). High blood pressure also causes microvascular diseases, which in turn can cause local ischemia of the tissue (6).

In addition to production of lactate, which inhibits the secretion of urate into proximal tubule, ischemia can increase the production of uric acid. Due to ischemia, ATP changes into adenine and xanthine and xanthine oxidase production increases, thereby increasing uric acid level (7). That ischemia causes a rise in uric acid may explain why uric acid level increases in preeclampsia as well as congestive heart failure (9). However, new experimental findings have inspired a reinterest in the possible role of uric acid in pathogenesis of hypertension and cardiovascular diseases. Invitro biochemical data also show that uric acid, often known as an antioxidant, causes the formation of free radicals, increases lipid oxidation and exerts various prooxidant effects on vascular cells.

Invivo and invitro findings suggest that uric acid may be involved in endothelial dysfunction by exerting proliferative effects on endothelium and disturbing nitric oxide production. The pro-inflammatory and proliferative effects of uric acid on vascular smooth muscle cells have been described, and hypertension has been reported to occur in animal models with mild hyperuricemia owing to inducing intrarenal vascular diseases. The aberrant effects of uric acid on vascular system have been known to be associated with increase of chemokines and cytokines, activation of renin-

angiotensin system and increase of CRP (10). Allopurinol can reduce uric acid by inhibiting xanthine oxidase enzyme, thereby altering the activity of renin and nitric oxide and leading to improved endothelial performance. The association of uric acid with endothelial dysfunction and increased performance of renin has also been shown in human (11, 12).

Since few studies have been performed on the relationship of uric acid with blood pressure in the patients with end-stage renal disease (ESRD), this study was aimed to evaluate the effects of allopurinol administration on serum uric acid and blood pressure of the patients under hemodialysis.

Materials and methods

This double-blind clinical trial was conducted on the hemodialysis patients at Imam Reza hospital, Kermanshah in 2014. The study population comprised of hemodialysis patients suffering from hyperuricemia (UA≥7 mg/dl in men and UA≥6 mg/dl in women) and hypertension whose blood pressure was not controllable despite receiving a full dose of antihypertensive drugs (calcium canal inhibitors, alpha blockers and angiotensin-converting enzyme inhibitor). Some of these patients consumed one or two types of drug due to several reasons, especially medication side effects. Thus, a total of 146 patients were included in the study considering the inclusion and exclusion criteria.

The inclusion criteria consisted of the hemodialysis patients with a history of at least three months, lack of using uric acid reducing drugs and lack of using diuretics. The exclusion criteria, however, included lack of regular referral of the patient and creating severe side effects leading to termination of drug consumption. At the beginning of the study, informed consent was taken from all participants. The patients were then assigned to two groups through simple random sampling. The first group (case group) received a daily dose of 100 mg allopurinol as uric acid reducer and the second group (control group) received placebo.

Over the course of study, the patients not fulfilling the inclusion criteria were excluded from the study and finally 62 samples in the patient group and 70 samples in the control group remained as the study sample. It should be noted that allopurinol was manufactured by Hakim and placebo was manufactured by the faculty of pharmacy. Both groups received standard measures of hemodialysis and antihypertensive drugs they used to take.

At the beginning of the study, a checklist was completed for each patient, including demographic information (height, weight, gender, education, history of smoking, and dialysis duration), vital signs, paraclinical data (serum uric acid, creatinine, blood urea nitrogen, hematocrit, serum albumin, cholesterol, triglyceride, and fasting blood sugar) and comorbidities (cardiac failure, coronary artery diseases, cardiac arrest, heart attack, cardiac arrhythmia, cerebrovascular diseases, peripheral vascular disease, diabetes, chronic obstructive pulmonary disease, mobility disability, and inability to move). After administration of the prescribed drugs at the end of the first, second and third months, the serum uric acid level and blood pressure were measured again. Blood pressure measurement was performed according to the standard protocol (13). Data were fed into SPSS-16 software and analyzed by descriptive (mean and standard deviation) and inferential statistics (t-test, chi-square, paired t-test and repeated measure t-test).

The sample size was calculated to be 73 samples in each group according to the following formula with 95% confidence interval and 80% test power, where $Z_{1-\alpha/2}$=1.96, $Z_{1-\beta}$ =0.84, S_1=1.31, S_2=1.03, $\overline{X_1}$=7.07 and $\overline{X_2}$=6.52 (14).

Results

In this study, 24 men and 38 women, with the mean age of 55±3.7, were allocated to the case group and 30 men and 40 women, with the mean age of 57±4.5, were assigned to the control group. Chronic renal dysfunction in both groups was due to hypertension, diabetes, glomerulonephritis and urinary reflux. It is worth noting that both groups were reported not to have a significant difference with each other with regard to demographic characteristics. The mean and standard deviation of each group as well as the results of t-test for independent groups at each time are presented in Table 1.

Table 1 shows the mean and standard deviation of systolic and diastolic blood pressure in the case and control groups at different times. As indicated, there was no significant difference between the case and control groups in pre-dialysis systolic and diastolic blood pressure and post-dialysis diastolic blood pressure before intervention. However, the systolic blood pressure showed a significant difference after dialysis (Table 1).

Table 1. Mean and standard deviation of systolic and diastolic blood pressure before and after dialysis at different measurement times

		Before intervention	P-value	One month after intervention	P-value	Two months after intervention	P-value	Three months after intervention	P-value
Pre-dialysis systolic blood pressure	Case	165.80±12.22	P=0.86	155.80±5.90	P<0.001	149.03±8.73	P<0.001	146.45±9.76	P<0.001
	Control	165.42±10.02		163.71±9.03		162.28±9.95		161.71±7.00	
Post-dialysis systolic blood pressure	Case	158.70±12.47	P=0.01	149.67±12.67	P=0.28	141.29±9.14	P<0.001	141.93±10.05	P<0.001
	Control	154.00±8.05		151.71±8.84		149.42±8.99		150.28±8.15	
Pre-dialysis diastolic blood pressure	Case	100±6.77	P=0.36	95.80±4.97	P<0.001	93.22±5.94	P<0.001	92.58±6.97	P<0.001
	Control	99.14±3.70		100±3.40		98.85±4.67		98.57±3.52	
Post-dialysis diastolic blood pressure	Case	96.61±5.30	P=0.054	93.54±6.00	P=0.29	90.64±6.74	P=0.02	90.00±6.27	P=0.03
	Control	94.85±5.00		94.57±5.00		92.85±4.55		92.85±4.55	

To analyze the differences at various times of measurement, repeated measure of analysis was run whose results are presented below for the case and control groups before and after dialysis, i.e. before intervention and one month, two months and three months after intervention.

Pre- and post-dialysis systolic blood pressure

As for the means of pre-dialysis systolic blood pressure, no significant difference was found between groups prior to intervention (p=0.86). The results of repeated measure analysis showed a significant effect for the time (p<0.001, f=51.20) as well as time-group interaction (p<0.001, f=23.66), so that the systolic blood pressure reduced by 19.35 in the case group as the time passed, but it declined by 3.71 in the control group. The results of sphericity test indicated the significant effect of time and group-time interaction for systolic blood pressure. The between-group analysis also showed a significant difference between groups in terms of systolic blood pressure (p<0.001, f=57.61). Therefore, a significant difference was reported between study groups at different times of measurement. The findings of Bonferroni test showed that the total mean of pre-dialysis systolic blood pressure of both groups in the third month was reduced by 11.5 compared with the value obtained before intervention, indicating a significant difference (p<0.001).

The mean post-dialysis systolic blood pressure before intervention was found to be significantly different between the case and control groups (p=0.01). Thus, the scores obtained before intervention were defined as covariates in order to control the effect of scores before intervention. The results of repeated measure analysis were reported according to statistical control. Also, the differences were shown by figures with all measurements. The findings of repeated measure tests showed a significant effect for time (p=0.04, f=3.18), time-group interaction (p=0.01, f=4.27), and pre-intervention-time measurement interaction (p=0.02, f=3.94), so that it was reduced by 16.75 in the case group with the passage of time while it declined by 3.71 in control group. The results of sphericity test revealed a significant effect for the time-group interaction (p=0.01, f=4.28) and time in the case of diastolic blood pressure (p=0.007, f=0.05). The results of between-group analysis also showed a significant difference between groups with regard to diastolic blood pressure (p<0.001, f=50.66). These changes are demonstrated in figure 1.

Pre- and post-dialysis diastolic blood pressure

As for pre-dialysis diastolic blood pressure, no significant difference was observed between the case and control groups in the pre-test (p=0.36). The results of repeated measure analysis indicated a significant effect for time (p<0.001, f=18.72) and time-group interaction (p<0.001, f=18.20), so that with the passage of time diastolic blood pressure was reduced by 7.42 in the case group and by 0.57 in the control group. Further, the findings of sphericity test showed a significant effect for time (p<0.001, f=24.05) and time-group interaction (p<0.001, f=17.89) in diastolic blood pressure. The results of between-group analysis also indicated a significant difference between study groups regarding diastolic blood pressure (p<0.001, f=38.54). Thus, there was a significant difference between various groups at different times of measurement. The findings of Bonferroni correction showed 3.99 reduction for mean pre-dialysis diastolic blood pressure of both groups three months after intervention compared with the value obtained before intervention, indicating a significant level compared to the baseline (p<0.001).

The mean post-dialysis diastolic blood pressure showed a significant difference between the case and

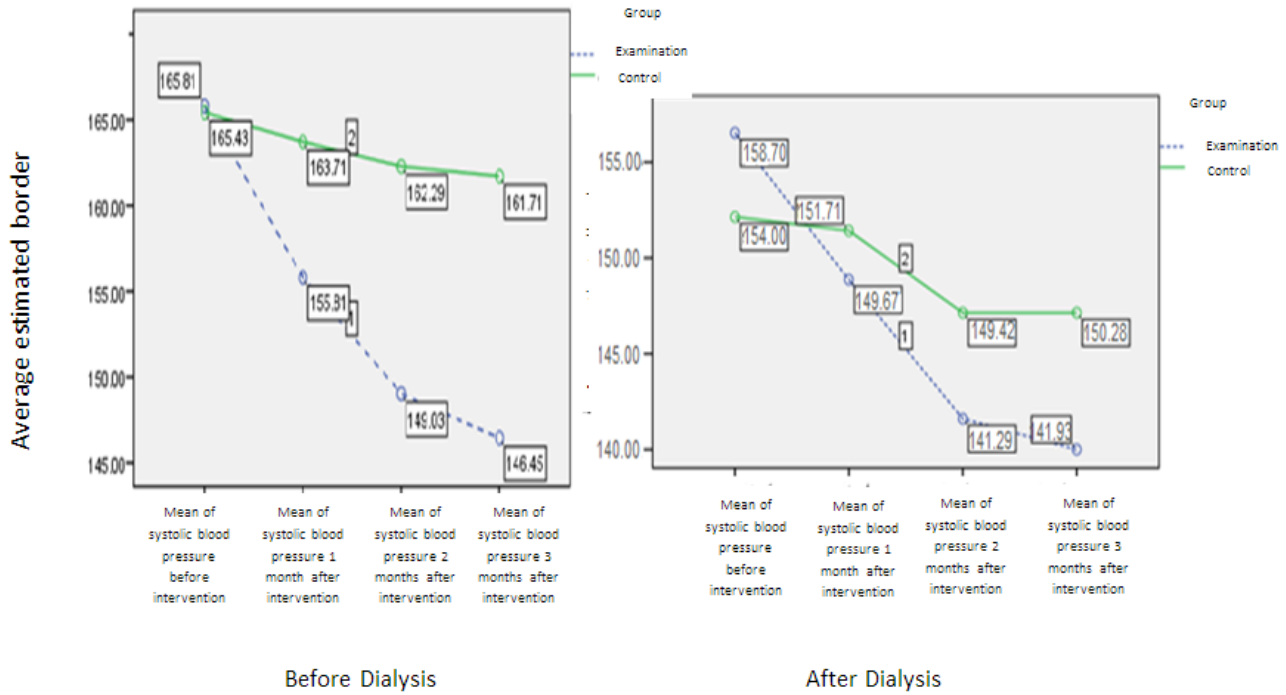

Figure 1. Pre- and post-systolic blood pressure at different times of measurement in both groups

control groups in the pre-test (p=0.054). Moreover, the repeated measure analysis indicated a significant impact for the time (p<0.001, f=22.39), time-group interaction (p=0.01, f=6.24), and pre-intervention-time interaction (p=0.02, f=3.94), revealing 6.61 reduction in the case group and 2 in the control group over time. Also, the results of sphericity test indicated a significant effect for time (p<0.001, f=29.90) and time-group interaction (p<0.001, f=7.53) for diastolic blood pressure. The results of between-group analysis also showed a significant difference between study groups with regard to diastolic blood pressure (p=0.012, f=2.39). Furthermore, Bonferroni correction revealed 4.30 reduction for the mean post-dialysis diastolic blood pressure of both groups three months after intervention in comparison with the value obtained before intervention, which was statistically significant (P<0.001). The details of these findings are shown in figure 2.

Uric acid

The results of multivariate analysis showed a significant effect for the time (p<0.001, f=37.62) and time-group interaction (p<0.001, f=30.46) regarding uric acid. Sphericity test also indicated a significant difference in terms of time (p<0.001, f=37.62) and time-group interaction (p<0.001, f=37.62). Moreover, the between-group analysis revealed a significant difference between study groups (p<0.001, f=28.29). The mean, standard deviation and significance level of uric acid at different times are presented in Table 4.

Also, uric acid changes at different times of measurement are presented in Figure 3.

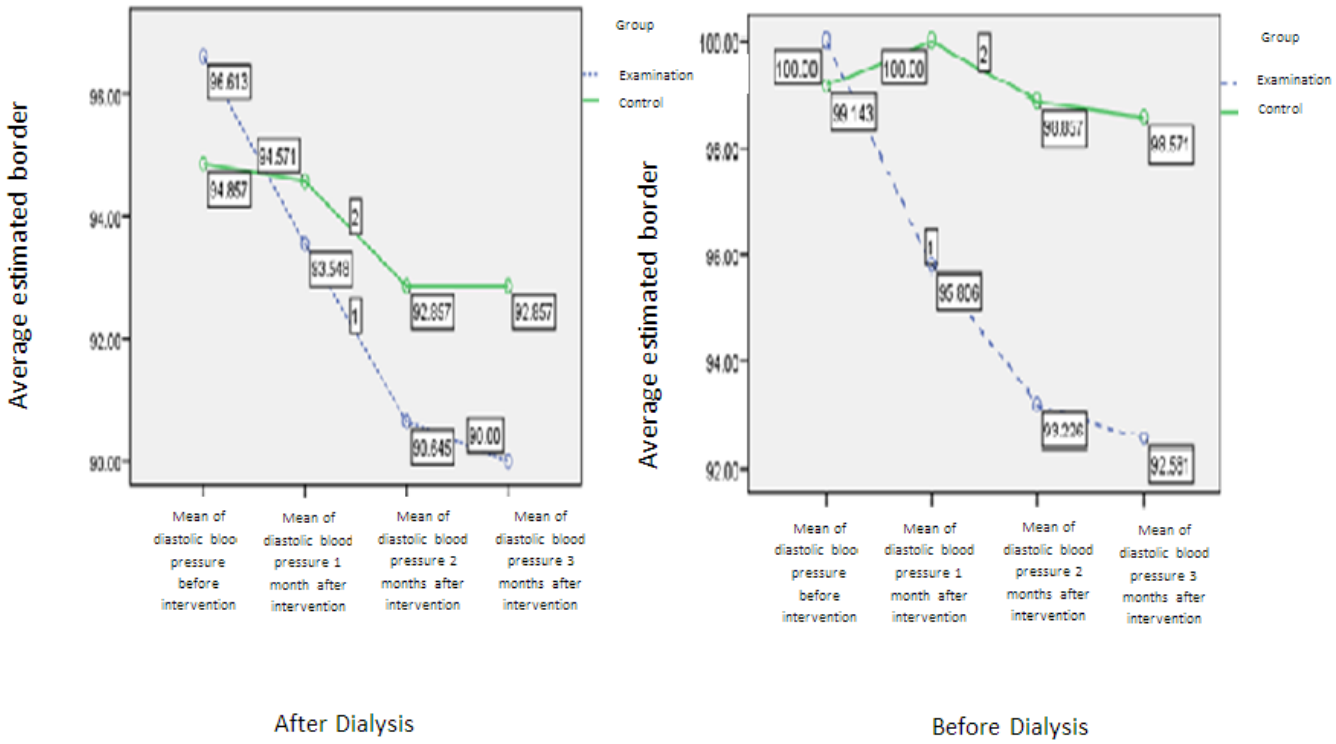

Figure 2. Pre- and post-diastolic blood pressure at different times of measurement in both groups

Table 2. Mean and standard deviation of uric acid independent groups at different times of measurement

Variable	Group	Mean	SD	P-value
Uric acid before intervention	Case Control	7.51 7.36	0.98 0.86	P=0.35
Uric acid one month after intervention	Case Control	6.21 7.09	1.11 0.76	P<0.001
Uric acid two months after intervention	Case Control	6.34 7.12	1.20 0.93	P<0.001
Uric acid three months after intervention	Case Control	5.90 7.40	1.13 0.8	P<0.001

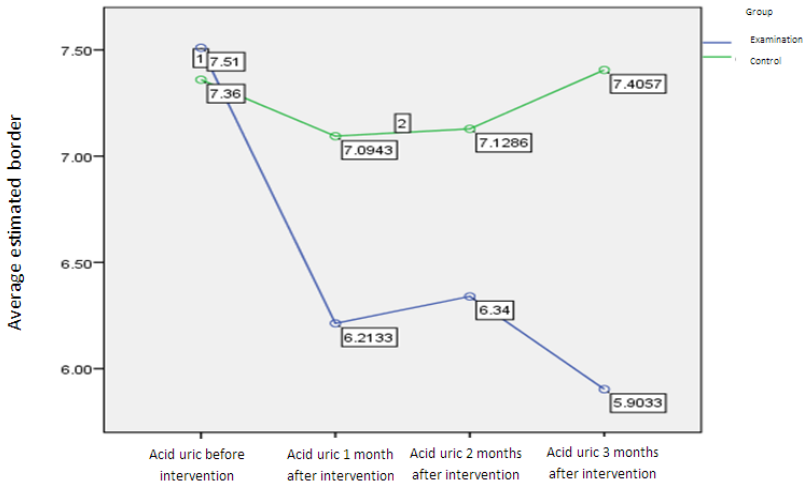

Figure 3. Uric acid changes at different times of measurement in both groups

Discussion and conclusion

The majority of hemodialysis patients suffer from hypertension. Hypertension causes the risk of left ventricular hypertrophy, coronary artery diseases, congestive heart failure and cerebrovascular disease. Hypertension is multifactorial in this group of patients and antihypertensive drugs cannot adequately control the blood pressure level (16-20). Hypertension is much prevalent in hemodialysis patients, among whom 70% have been estimated to suffer from hypertension, which is accompanied by annual mortality rate of 23% (16, 18, 21).

It is generally believed that hypovolemia due to accumulation of fluid and salt is the major cause of hypertension in the patients under hemodialysis (18, 21-22). Blood pressure control can reduce mortality in these patients (16, 18, 21, 13). Lowering the blood pressure in these patients should be initially performed by limiting the salt and approaching dry weight and then by antihypertensive drugs. Hyperuricemia is an indicator of hypertension and is usually available in newly-initiated essential hypertension (1). Further, hyperuricemia is associated with coronary artery diseases and renal dysfunctions (11-24). Uric acid is also known as the end product of purine catabolism associated with diabetes and atherosclerosis (11).

Recent studies have suggested that uric acid is an independent risk factor associated with renal diseases, especially among the patients with hypertension (11, 27). The mechanism by which uric acid impairs the organisms is unknown, but there is increasing evidence showing its mechanism to be endothelial cell dysfunction. Hypertension is continuously associated with endothelial cell dysfunction, and hyperuricemia is a potent predictor of hypertension induction and progress. In fact, high level of uric acid is associated with renal-oriented hypertension regardless of the renal involvement. It has been shown that allopurinol treatment reduces hypertension in adolescents with newly-diagnosed hypertension (11, 22, 28). These results are indicative of a potential treatment approach but need to be proved in larger trials.

There is no specific data concerning the correlation of uric acid and hypertension in hemodialysis patients. Tang et al. evaluated the relationship of uric acid and endothelial cell dysfunction in 189 patients under peritoneal dialysis and reported an independent association between uric acid levels and brachial artery flow-mediated dilation as indicator of endothelial cell dysfunction (29). Accordingly, Silverstein et al. analyzed the association between uric acid and hypertension among 36 children with hemodialysis and found a correlation between pre-treatment systolic blood pressure and high levels of uric acid. They concluded that serum uric acid independent of volume, nutrition and weight affects the blood pressure of patients (22). Moreover, Daniel et al. conducted a large clinical trial that was published in "The Journal of the American Medical Association". This hospital trial was carried out on thirty 11-37-year-old patients diagnosed with initial hypertension. The patients were found to have >6 uric acid level. After administration of allopurinol treatment regimen, the patients' blood pressure and uric acid were significantly reduced (30).

Furthermore, a recent study by Jalalzadeh et al. showed that reduced uric acid level caused a decline in the blood pressure of the hemodialysis patients with hypertension (15). In this clinical trial which was performed on 53 hemodialysis patients with hyperuricemia, it was concluded that allopurinol treatment significantly reduced systolic and diastolic blood pressure as well as uric acid in the patients. This was confirmed by Nasri in the same year and was introduced as a new and effective treatment regimen (31).

In the current study, we concluded that allopurinol decreases systolic and diastolic blood pressure in hypertensive patients under hemodialysis by lowering uric acid level, indicating a significant difference between the case and control groups. Therefore, it can be argued that allopurinol treatment regimen plays a pivotal role in reducing blood pressure and uric acid level of hemodialysis patients, thereby improving their life quality.

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