THE EFFECT OF ALLOPURINOL THERAPY ON BLOOD PRESSURE IN PATIENTS OF CHRONIC KIDNEY DISEASE WITH HYPERTENSION AND HYPERURICEMIA UNDERGOING HEMODIALYSIS

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ABSTRACT

Objective: To determine the effect of allopurinol therapy on blood pressure in patients of Chronic Kidney Disease with hypertension and hyperuricemia undergoing hemodialysis.

Study Design: Quasi experimental study.

Place and Duration of Study: Department of Medicine, Pak Emirates Military Hospital Rawalpindi, from Nov 2015 to May 2016.

Methodology: One hundred and seventy-two patients with the diagnosis of chronic kidney disease and on regular hemodialysis were selected after fulfilling the inclusion and exclusion criteria. The blood pressure of patient before and after dialysis was measured. The patients were given 100mg of allopurinol daily for three months. The blood pressure was checked weekly by the researcher before and after dialysis. The mean systolic and diastolic blood pressure before and after three months' treatment were compared using paired-sample t-tests. The efficacy was defined as attainment of blood pressure <140/90 mmHg at two readings 24 hours apart. The McNemar test was applied to see the efficacy of treatment at three months.

Results: Mean age of the sample was 46.6 ± 6.1 years. Out of 172 patients, 51.7% were males while 48.3% were females. The mean duration of chronic kidney disease was 3 ± 1.3 years. The mean systolic blood pressure was 160.7 ± 11.8 mmHg while diastolic blood pressure was 105.7 ± 8.8 mmHg at the start of study period. At the end of three months, the systolic and diastolic blood pressures were 139.6 ± 11.2 mmHg and 96.4 ± 13.6 mmHg respectively. At the endpoint, a significant number (113, 65.7%, p<0.001) of patients had blood pressure in the desired values i.e. <140/90 mmHg. The effect modifiers like age, gender, and duration of chronic kidney disease were tabulated against efficacy and the differences were found insignificant.

Conclusion: Allopurinol was effective for the control of blood pressure in our sampled patients, who were hypertensive and hyperuricemic and were undergoing regular hemodialysis.

Keyword: Allopurinol, Blood pressure, Chronic kidney disease, Hyperuricemia, Hemodialysis.

INTRODUCTION

Chronic kidney disease (CKD) is a type of kidney disease in which there is a gradual loss of kidney function over a period of months or years. The population prevalence of CKD exceeds 10%, and is more than 50% in high-risk subpopulations[1]. The prevalence could rise sharply over the next few decades, steered by population ageing and an increasing prevalence of diabetes and hypertension[2]. The etiology of CKD includes diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease, lupus, obstructions caused by problems like kidney stones, and repeated urinary tract infections. Hyperuricemia is also an independent risk factors for the development and progression of CKD[3].

Complications of CKD may include heart disease, hypertension, bone disease, hyperuricemia, or anemia. CKD is among a small number of diseases for which death rates have substantially risen since 1990[4]. Age-standardized mortality due to CKD increased by 36.9% from 11.6 deaths per 100,000 population in 1990 to 15.8 deaths per 100,000 population in 2013[4]. In 2015, it resulted in 1.2 million deaths worldwide[5,6]. Since

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hypertension and hyperuricemias have causal relationship for the development and progression of CKD, controlling hypertension and lowering the serum uric acid (UA) levels, is associated with a slowing in the rate of renal deterioration in patients with CKD[7-9].

Hyperuricemia and hypertension also contribute to each other[9]. Feig and Johnson found that about 90% of adolescent hypertension is associated with hyperuricaemia[10]. UA is produced by the action of xanthine oxidase on purines and has been shown to cause hypertension and arteriolopathy through activation of the renin-angiotensin system and inhibition of nitric oxide (a potent vasodilator) production. Xanthine oxidase activity also produces reactive oxygen species, namely superoxide, hydrogen peroxide, and the hydroxyl radical[11]. Reactive oxygen species cause tissue damage and inactivate nitric oxide, leading to endothelial dysfunction, atherosclerosis, vasoconstriction, and vascular injury. Allopurinol inhibits xanthine oxidase activity, reduces production of UA, improves the bioavailability of nitric oxide and thus results in lowering of blood pressure (BP).

In Pakistan, there is paucity of specific data on the relationship of serum UA levels and hypertension in the setting of CKD. The rationale of this study was to assess the efficacy of allopurinol in lowering BP of patients with CKD who had hyperuricemia and high BP and were undergoing hemodialysis. Evaluation of the role of effect modifiers like age, gender, and duration of CKD was a secondary goal.

METHODOLOGY

It was a quasi-experimental study carried out in the department of Medicine, Pak Emirates Military Hospital, Rawalpindi from November 2015 to May 2016. A sample size of 172 was calculated by the standard World Health Organization sample size calculator using confidence level of 95%, absolute precision of 5% and population proportion of 8.6%. The inclusion criteria were patients with CKD (Glomerular filtration rate (GFR) <15mL/min/1.73m^2) having hyperuricemia and hypertension and on hemodialysis for at least six months. Hypertension was defined as two or more readings of systolic BP >140 mmHg and diastolic BP> 90 mmHg on two or more consecutive visits for both gender groups. The hyperuricemia was defined as serum UA levels of >6.5 mg/dL in males and >5.5 mg/dL in females. The exclusion criteria were malignant hypertension i.e. BP>210/120 mmHg, allopurinol intolerance, patient already on allopurinol, active infections, and history of alcohol intake, gouty arthritis, renal stones, polycystic kidney disease, chronic liver disease, malignancy and pregnancy.

After permission from the concerned authorities and ethical committee, 192 patients, diagnosed with CKD, hyperuricemia, and hypertension, and on hemodialysis for the past six months, were selected through consecutive sampling. Detailed history was taken and thorough clinical examination was carried out. Hospital registration numbers and informed consent were taken from all patients. BP measurements were taken before and after dialysis at the time of recruitment. All the BP recordings were taken by the researcher using Yamasu Stand-Type Mercurial Sphygmomanometer model no: 620 after sitting in relaxed position for ten minutes. Twenty individuals were excluded after implementing the exclusion criteria.

One-hundred and seventy-two finally included patients were given allopurinol 100 mg (Zyloric, Glaxo Smith Kline Pakistan limited, Karachi, Pakistan) once daily, orally, for three months. Hemodialysis was done for four hours thrice weekly. Patients were followed weekly with BP measurements. During the study, the antihypertensive therapies were not altered. At the end of three months, BP was measured again before and after the dialysis. The average of the BP measure-ments was used instead of individual measurements before and after dialysis. The efficacy of allopurinol was defined by a reduction of BP to normal values taken as <140/90 mmHg. The data were recorded in especially designed proformas.

The data were analyzed using SPSS version 18 and web-based statistics analyzer Open Epi-version 3.03a. Means and standard deviations were calculated for quantitative data like age, serum UA levels, and systolic and diastolic BPs. The qualitative data like gender and efficacy were analyzed by frequencies and proportions. For the sake of simplicity, the average measurements of BP before and after dialysis were taken for the analysis. The mean systolic and diastolic BP before and after three months' treatment were compared using paired-sample t-tests. McNemar test was applied for the evaluation of efficacy at three months. Effect modifiers like age, gender, and duration of CKD were controlled by stratification. The sample was divided into two groups based on age i.e. (age ≤50 years, and age >50 years) and duration of CKD (duration ≤2 years and duration >2 years). After stratification, chi-square test was applied. A *p*-value ≤0.05 was considered significant.

RESULTS

A total of 172 patients were included. Mean age of the sampled patients (n=172) was 49.6 ± 6.1 years. There were 91 (52.9%) individuals ≤50 years of age and 81 individuals >50 years of age. Eighty-nine (51.7%) were males while eighty-three (48.3%) were females. The serum UA levels at the start of study period were 8.6 ± 1.2 mg /dL collectively. The baseline mean systolic BP was 160.7 ± 11.8 mmHg while diastolic BP was 105.7 ± 8.8 mmHg. The mean duration of CKD was 3 ± 1.3 years. Sixty-seven (39%) individuals had been diagnosed with CKD for ≤2 years' duration while 105 (61%) were diagnosed with CKD for >2 years' duration.

Table-I: Table showing efficacy of allopurinol at three months post treatment.

Treatment stage	Efficacy (Blood pressure <140/90 mmHg)		*p*-value
	Yes	No	
At start	-	172 (100%)	<0.001
At three months	113 (65.7%)	59 (34.3%)	

Table-II: Table showing comparison of allopurinol effect on blood pressure based on age-group, gender, and duration of chronic kidney disease.

Parameters		Target achieved at three months		*p*-value
		Yes (n%)	No (n%)	
Age	≤50 yrs	56 (61.5)	35 (38.5)	0.224
	>50 yrs	57 (70.4)	24 (29.6)	
Gender	Male	59 (66.3)	30 (33.7)	0.865
	Female	54 (65.1)	29 (34.9)	
Duration of Chronic kidny disease	≤2 yrs	42 (62.7)	25 (37.3)	0.506
	>2 yrs	71 (67.6)	34 (32.4)	

After three months, the systolic BP significantly decreased from 160.7 ± 11.8 to 139.6 ± 11.2 mmHg (p<0.001) and diastolic BP from 105.7 ± 8.8 to 96.4 ± 13.6 mmHg (p<0.001). Considering the target parameter, a significant (p<0.001) reduction of BP to normal (efficacy) was seen in 113 (65.7%) while no reduction was seen in 59 (34.3%) (table-I).

The data were stratified according to age, gender, and duration of CKD. All these variables were compared with the efficacy of allopurinol. No significant association of efficacy with age, gender or duration of CKD was observed (table-II).

DISCUSSION

Allopurinol is a xanthine oxidase inhibitor that inhibits conversion of hypoxanthine to xanthine and then xanthine to UA without disruption of synthesis of vital purines[12-14]. The effect of allopurinol is evident in 2-3 days. It has a peak plasma time of 0.5-2 hours while 7-14 days are needed for the peak effect[14]. It is metabolized in the liver into "oxypurinol" that is an active metabolite and then both substrates act to inhibit xanthine oxidase and thus reduce UA levels in the body[14]. The serum UA levels are positively correlated with the BP measurements in CKD patients. Reduced serum UA levels lead to deactivation of renin-angiotensin system and increased availability of nitric oxide, which further lowers BP in patients with CKD. In this study, we also found a significant reduction in BP at three months of 100mg allopurinol therapy in CKD patients with hyperuricemia and on hemodialysis. In a similar study, Jalalzadeh *et al*[13] studied the effects

of allopurinol on lowering BP in an Iranian cohort. The study was a cross-over trial. In the first phase, 100 mg/day allopurinol for three months was used in one group while the other group continued the same medications they were already taking for hypertension. After two months of washout period, the groups were reversed. The UA levels decreased significantly during the total 12 weeks of allopurinol therapy (7.71 ± 1.53mg /dL to 5.2 ± 1.2mg /dL, p<0.005). Overall, the systolic and diastolic BP also significantly decreased in the allopurinol groups; 15.8% (139 mmHg to 117 mmHg, p<0.0005) and 8.6% (81 mm Hg to 74 mmHg, p<0.0005), respectively. Kanbay *et al*[15] also observed a significant reduction (p <0.05) in serum UA levels, GFR, systolic and diastolic BP, and C-reactive protein levels in 59 patients at three-month's follow-up following allopurinol treatment.

In another trial, Satirapoj *et al*[16] found that allopurinol decreased BP and improved renal functions in patients with early stage kidney disease. This study had small sample size as compared to our study (44 versus 172) and lower dose of allopurinol (50 versus 100 mg/day for 12 weeks). The study revealed that allopurinol significantly lowered the systolic BP (137.72 ± 14.72 mmHg to 131.34 ± 12.10 mmHg, p=0.019) and the diastolic BP (79.63 ± 11.56 mmHg to 75.43 ± 9.80 mmHg, p=0.037) at 12 weeks when compared to the baseline. The contrasting feature of our study was inclusion of only the hypertensive patients. This factor might have been responsible for more significant difference at conclusion of our study.

There are, however, other studies that have observed the contradictory results of allopurinol treatment on BP. Goicoechea *et al*[17] randomized 113 patients with eGFR <60mL/ min/1.73 m^2 to allopurinol or usual treatment for 24 months. There was a positive effect on eGFR but no effect on BP. Siu *et al*[18] trialed 54 hyperuricemic patients with use of 100 to 300 mg of allopurinol for 12 months. There was no effect on the systolic and diastolic BP after allopurinol therapy, though there was a decrease in serum UA levels.

In our study, we analyzed the data by stratification also. The stratification was done to observe the influence of effect modifiers like age, gender, and duration of CKD. The results showed that there was no significant difference between the stratification groups in terms of allopurinol efficacy.

The protective role of allopurinol for preservation of renal functions has been demonstrated in many studies[19-21]. In 2014, Sezer *et al* showed the role of allopurinol on cardiovascular risks and renal functions in pre-dialysis patients with hyperuricemia[21]. This study suggested the role for allopurinol as a reliable therapeutic option in controlling renal progression in pre-dialysis CKD patients. Allopurinol is also effective in patients of diabetes mellitus for the protection of renal damage. Allopurinol produces long-term effective control of serum UA levels, which decreases serumcreatinine, increases GFR, and may exert kidney protection effects in patients with type 2 diabetes and asymptomatic hyperuricemia[22].

Hyperuricemia is an independent risk for hypertension and the risk appears to be more pronounced in younger individuals and in women[23]. In patients with CKD, accordingly, an association of high systolic BP with a high serum UA level, independent of volume, nutritional status, and body weight has been observed[24]. However, a strict audit of the quality of these studies does not recommend use of allopurinol just for the sake of reducing BP in CKD patients especially when they are on hemodialysis[9]. Moreover, allopurinol use is associated with side effects that include rash, nausea, vomiting, arthralgias, bronchospasm, iritis, neuritis, blood dyscrasias, hepatic toxicity, and renal failure. The drug also has serious interactions with azathioprine, captopril, enalapril, theophylline, didanosine, and warfarin[14], in view of that, an alternative choice has to be opted for continuation of positive medicinal effects. Thus, use of allopurinol for the sole management of high BP in CKD is not suggested. If allopurinol has to be used, it should be started in a low dose and then the dose is titrated with the serum UA levels. The dose

ought to be adjusted according to effects and the renal functions[25].

CONCLUSION

Allopurinol was effective for the control of BP in our sampled patients, who were hypertensive and hyperuricemic and were undergoing regular hemodialysis. No influence of age, gender, and duration of CKD was found on the results. The results, however, need further evaluation by large randomized controlled trials.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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