

Efficacy of high dose Allopurinol in reducing left ventricular mass in patients with left ventricular hypertrophy by comparing its efficacy with Febuxostat — a randomized controlled trial

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Abstract

Objective: To determine the efficacy of high-dose allopurinol in reducing left ventricular mass in patients with left ventricular hypertrophy by comparing its efficacy with febuxostat.

Methods: The randomised controlled interventional study was conducted at Mayo Hospital, Lahore, Pakistan, from April to December 2015, comprising patients with left ventricular hypertrophy on echocardiography. They were randomly divided into two equal groups, with Group A receiving allopurinol and Group B receiving febuxostat. Primary endpoint was reduction in left ventricular mass and left ventricular mass index as calculated by echocardiography. Patients were followed at third and sixth month of enrolment to detect regression. Patients were investigated for eosinophil's count, urine for micro albuminuria and renal function tests to monitor side effects of allopurinol. SPSS 20 was used for data analysis.

Results: There were 76 patients divided into two groups of 38(50%) each. Mean reduction in left ventricular mass between baseline and at six months in Group A and Group B was 35.474 ± 13.54 and 21.921 ± 3.33 respectively ($p=0.0001$) while mean reduction in left ventricular mass index between baseline and at six months was 17.26 ± 4.36 and 17.63 ± 21.07 respectively ($p=0.0001$). Greater improvement was observed in Group A.

Conclusion: Allopurinol was found to be more effective than febuxostat in reducing the left ventricular mass and left ventricular hypertrophy independent of blood pressure.

Keywords: Allopurinol, Febuxostat, Left ventricular mass, Left ventricular mass index. (JPMA 68: 1446; 2018)

Introduction

Cardiovascular disease is a leading cause of death globally, resulting in about 30% of the deaths annually.¹ Left ventricular hypertrophy (LVH) is a strong predictor of cardiovascular mortality. LVH predates many cardiovascular events such as arrhythmias, diastolic heart failure, left atrial enlargement and atrial fibrillation.² LVH is a widespread finding even in patients with normal blood pressure. Longitudinal data has validated results of previous cross-sectional studies, indicating that left ventricular mass (LVM) progressively increases over time with progression increases in the presence of risk factors like diabetes mellitus (DM), hypertension (HTN) and obesity.^{3,4} Early diagnosis and treatment of LVH is important for two reasons; firstly it is a long-recognised adverse prognostic value, and, second, its ability of regression.⁵ LVH is diagnosed by either of the three diagnostic tools; electrocardiography (ECG), echocardiography or cardiac magnetic resonance imaging (MRI) which is the gold standard. The accuracy of echocardiographic M

mode, in detecting LVH by using interventricular septum thickness, posterior wall thickness and end diastolic diameter of left ventricle (LV), is adequate compared to ECG and 2D echocardiographic mode.⁶ Prevalence of echocardiographic LVH is different in different populations and varies from 20% to 70% based on criteria used and population studied.⁷ Irrespective of gender, LVH occurs as a result of adverse ventricular remodelling patterns like concentric and eccentric remodelling.⁸ Concentric LVH is more commonly seen in pressure overload conditions like HTN, while eccentric LVH is more common among the obese and the aging.⁹ A novel strategy to prevent development of LVH and to halt its progression is of great importance, especially for a large population suffering from chronic co-morbid illnesses like ischaemic heart disease (IHD), DM, HTN, chronic kidney disease (CKD) and obesity. Different pharmacological agents are used for regression of LVH like angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, calcium channel blockers and β -blockers. According to a study, ACE inhibitors reduce LV mass by 15%. Lesser reduction was achieved with diuretics (11%), β -blockers (8%), and calcium-channel blockers (8.5%).¹⁰ Recent studies have shown

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that allopurinol also significantly reduces LV mass, by improving vascular endothelial function through its anti-ischaemic effects and by reducing end systolic volume.¹¹ There is strong basic scientific evidence that LVH is the result of myocardial remodelling, myocyte hypertrophy and myocardial fibrosis.¹² Reactive oxygen species, such as hydrogen peroxide and superoxide, are produced by xanthine oxidase.¹³ Drugs like allopurinol and febuxostat inhibit xanthine oxidase to reduce oxidative stress which results in LVH reduction.¹⁴ In addition, Dundee et.al has already reported the role of allopurinol in the regression of LVH in CKD and IHD patients.^{11,15} International data on the role of allopurinol in reducing LV mass both in CKD and in patients with normal renal functions is available but local literature is lacking.^{11,15} The current study was planned to fill that knowledge gap.

Patients and Methods

The randomised controlled interventional study was conducted at Mayo Hospital, Lahore, Pakistan, from April to December 2015 after approval from the institutional review board. The sample size was calculated by using 95% confidence interval (CI), 90% power of test and by taking expected mean percentage of reduction in LVM with allopurinol as -5.2 ± 5.8 and with febuxostat as -1.3 ± 4.48 .¹⁰ The sample was raised using non-probability purposive sampling. Consent was taken from every patient. Those included were patients of either gender aged 18-65 years with LVH diagnosed on echocardiography using American Society of Echocardiography criteria⁹ taking conventional treatment for LVH. Patients having hypersensitivity to allopurinol or febuxostat (on the basis of history), having congenital heart diseases, glomerular filtration rate (GFR) <60 ml/min/kg, already on allopurinol or febuxostat taking for gout and taking

other LVH regressing medications other than mentioned in the initial treatment were excluded. The selected subjects were randomly assigned to either the allopurinol Group A or the febuxostat Group B group by using the lottery method. All patients in both groups underwent echocardiography to assess LVM at presentation. In Group A, patients were given 100mg allopurinol along with conventional treatment initially for two weeks. In case of tolerance to allopurinol, it was then titrated up to dose of 600mg. In Group B, patients were given conventional treatment plus febuxostat 40mg. Outcome data was collected via serial direct contact visits with the patients every twelve weeks at an outpatient clinic until February 2016. All patients were followed up for a median of 7 months (range: 6-9 months) to find out the incidence of cardiac events, renal problems and serum uric acid levels. The primary endpoint was the echocardiographic LVM reduction after treatment. The LVM was measured at baseline (before treatment) and after three and six months of treatment along with eosinophil count, serum uric acid and renal function tests.

Data entry and analysis was done using SPSS 20. Quantitative data was presented as mean \pm standard deviation (SD). Qualitative data was presented as frequencies and percentages. One-way multivariate analysis of variance (MANOVA) was used to compare the groups regarding LVM and left ventricular mass index (LVMI) at 1st and 3rd visits. Wilks Lambda test was applied to calculate the significance of difference between the groups.

Results

There were 76 patients divided into two groups of 38(50%) each. All (100%) patients in both the groups completed the study. The mean age was 58.74 ± 9.43

Table-1: Clinical and biochemical characteristics in both groups at baseline and at six months.

	Allopurinol Group A (n=38)		Febuxostat Group B (n=38)	
	Baseline	At 6 months	Baseline	At 6 months
Mean age (in years)	58.74 \pm 9.43		57.32 \pm 12.79	
Gender	Male: 20 Female: 18		Male: 22 Female: 16	
Height (in Meters)	1.62 \pm 0.04		1.61 \pm 0.05	
Weight (in Kg)	67.39 \pm 6.8	67.10 \pm 6.5	67.91 \pm 8.93	67.66 \pm 8.85
Body mass index (Kg/m ²)	25.30 \pm 2.40	25.20 \pm 2.30	25.57 \pm 3.12	25.50 \pm 3.20
Serum urea (mg/dl)	34.47 \pm 5.0	29.26 \pm 2.40	33.76 \pm 5.08	29.26 \pm 2.87
Serum creatinine (mg/dl)	0.78 \pm 0.23	0.55 \pm 0.17	0.7 \pm 0.19	0.52 \pm 0.16
Eosinophil count (%)	1.71 \pm 0.86	1.78 \pm 0.87	1.90 \pm 1.12	2 \pm 1.17
Microalbuminuria (mg/day)	20.92 \pm 4.74	23.43 \pm 6.21	18.11 \pm 4.42	21.43 \pm 6.03
Serum uric acid (mg/dl)	5.57 \pm 0.43	5.48 \pm 0.46	5.63 \pm 0.57	5.38 \pm 0.49

Table-2: Descriptive Statistics and Comparison of Left ventricular mass (LVM) and Left ventricular mass index (LVMI) at 1st and 6 months visit in Group A and Group B.

	Visit	Group-A (Allopurinol) (n=38)		Group-B (Febuxostat) (n=38)	
		Mean	SD	Mean	SD
Left ventricular mass (LVM)	1st	251.34	63.15	262.61	96.16
	6 months	215.87	57.99	240.62	85.81
	Wilks Lambda Significance			<0.0001	
Left ventricular mass index (LVMI)	1st	143.55	31.73	159.29	76.58
	6 months	126.29	27.37	141.66	55.51
	Wilks Lambda Significance			<0.0001	

Table-3: Descriptive Statistics and Comparison of mean reduction of Left ventricular mass (LVM) and Left ventricular mass index (LVMI) at baseline and 6 months between both groups.

	Group-A (n=38)		Group-B (n=38)		P value
	Mean	SD	Mean	SD	
Reduction in LVM	35.47	5.16	21.99	10.37	0.0001
Reduction in LVMI	17.26	4.36	17.63	21.07	0.0001

years in Group A and 57.32 ± 12.79 years in Group B. There were 20(53%) males in Group A and 22(58%) in Group B. There were no significant difference between the groups in terms of gender, age, baseline body mass index (BMI) or baseline blood chemical variables (Table-1). Mean reduction in LVM between baseline and at six months in Group A and Group B was 35.474 ± 13.54 and 21.921 ± 3.33 respectively ($p=0.0001$) while mean reduction in LVMI between baseline and at six months was 17.26 ± 4.36 and 17.63 ± 21.07 respectively ($p=0.0001$) (Table-2). Greater improvement was observed in Group A (Table-3).

Discussion

Febuxostat and allopurinol are novel non-purine selective inhibitors of xanthine oxidase that has been shown to attenuate the production of reactive oxygen species and reduce the LV mass in patients with LVH. Previous studies suggest that both allopurinol and febuxostat may confer benefits for patients with LVH and hyperuricaemia. However, the current study made a direct comparison between allopurinol and febuxostat reducing LVM in patients with LVH. It revealed that allopurinol caused reduction in LVM and regression of hypertrophy in patients with LVH. Also, allopurinol caused greater reduction in patients having higher baseline LVM. It provides the first evidence that allopurinol treatment significantly improved cardiac function compared to febuxostat. In addition, the decrease in LVMI from baseline to 6 months in the allopurinol group was indicatively detected as collated to febuxostat group. Mean reduction in serum uric acid

level was higher and significant in febuxostat group. Both groups were similar in terms of having developed no adverse effects. However, allopurinol was more benign even when used at higher doses and for longer duration. Both drugs did not significantly affect urea, creatinine, eosinophil count and albumin in urine. In this study, reduction in LVM was higher compared to previous studies;¹⁵ probably it is because of selection of cases with higher baseline LVM at presentation. However, conclusion of study agrees with previous studies of LVH regression in ischaemic heart disease in which allopurinol also caused regression in LVH without altering the blood pressure.¹⁵ Other studies, done in animal models, have shown similar results.^{16,17} Whole work done so far marks allopurinol as a first drug that has shown categorical retrogression of LVH in human beings in many diseases, including IHD, DM, CKD and HTN. Finally, LVH regression is linked with reduction in cardiovascular morbidity and mortality apart from blood pressure changes,¹⁸ supported by the leading Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial, in which patients having HTN and ECG-proven LVH were studied.^{19,20} The LIFE study concluded that regression in LVH, regardless of reduction in blood pressure, was linked with lowering of all-cause mortality, sudden cardiac death, heart failure, myocardial infarction and cerebrovascular accidents.^{19,20}

Question to be answered is, how allopurinol regresses LVH. Allopurinol inhibits xanthine oxidase system involved in the production of reactive oxygen species, resulting in decrease in tissue oxidative stress,²¹ and oxidative stress is an intercede of ventricular hypertrophy.^{22,23} Therefore, theoretically, the diminution in oxidative stress could interpose regression in LVH. A clinical trial on 60 heart failure patients compared the effects of oxypurinol versus placebo in improving ejection fraction when added to standard therapy. It concluded that inhibition of xanthine oxidase by oxypurinol in heart failure patients improved left ventricle ejection fraction (LVEF) in

patients with LVEF less than or equal to 40% after 1 month of treatment.²⁴ The findings in the current study are parallel with the results of the cited trial²⁴ and means that the reduction in reactive oxygen species with allopurinol can have favourable effects on cardiac hypertrophy without the requirement of reducing blood pressure.

A study in diabetic patients with LVH checked the effects of allopurinol in the reduction of LVM by using cardiac MRI. Results showed that allopurinol did a significant reduction in absolute LVM and LVMI.²⁵ The study concluded that allopurinol caused significant reduction in LVM in patients having LVH. These findings are similar to the results of the current study.

Rekraj et al. studied the effect of high-dose allopurinol on LVH and endothelial function in patients with chronic stable angina. Results showed that LVM and LVMI decreased in the allopurinol group compared to the group on placebo, showing a momentous difference. They also suggested that allopurinol not only caused improvement in endothelial function, but also less vascular remodelling.¹⁵

All the above-mentioned studies provide strong logical basis regarding the role of allopurinol as an antioxidant. Allopurinol 600 mg/day was used in this study because of its dose-response relationship. Many studies used allopurinol in higher dose of 300 mg/day.¹¹ One study showed achievement of additional 52% improvement in endothelial function when allopurinol was used 600 mg/day.²¹ Allopurinol was well tolerated in the current study in the dose of 600 mg/day. The maximum dose of allopurinol is up to 900 mg/day.²⁶ Reassuringly, the current study also found that long-term use of allopurinol in high dose had no adverse effect on renal function.

In terms of limitations, the current study was conducted at a single centre with a small sample size. Besides, the efficacy of allopurinol was determined with conventional treatment and echocardiography was used instead of cardiac MRI which is more sensitive. Further multi-centred trials are warranted to endorse the results of the current study.

Conclusion

Allopurinol was found to be more effective than febuxostat in reducing the LVM, and may improve cardiac function in LVH patients, at least in part due to reductions in oxidative stress and improvements in endothelial dysfunction, resulting in better end diastolic dysfunction. Moreover, allopurinol was well

tolerated by patients even at higher doses used in the study.

Disclaimer: The manuscript was part of a Master's degree thesis in Medicine. Due to non-availability of a registration office for Randomized Control Trials in Pakistan, this study, a RCT, could not obtain a Trial Number and had only an approval from the Institution's Ethical Review Board.

Conflict of Interest: None.

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