Allopurinol Lowers Blood Pressure, Uric Acid

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Allopurinol Lowers Blood Pressure, Uric Acid and Endothelin-1 in Hypertensive Patients with Hyperuricemia at Mohammad Hoesin Hosiptal, Palembang, Indonesia

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Abstract: *Scientific reports suggesting a link between hypertension and hyperuricemia are considerable. However, little is known whether drugs that had proven to be effective in reducing uric acid will also efficative to overcome hypertension? To answer the question a* clinical trial *using allopurinol has been employed on the hypertensive patients with asymptomatic hyperuricemia. A total of 40 patients that fulfilled inclusion criteria, were separated by double-blind randomization into two groups, the allopurinol and placebo. The allopurinol-treated patients included 9 males and 11 females, while placebo consist of 10 males and 10 females. To each patient of both groups were given one capsule containing 100 mg of allopurinol for allopurinol group or non-active substance for placebo group for a month. Before and after trials the systolic as well as diastolic pressure, endothelin (ET)-1 uricacid levels of the subjects were assessed. The results showed patients treated with allopurinol siginicantly lower in systolic pressure (P=0.013), diastolic pressure (P=0.012), uric acid levels (P<0.001) and ET-1 levels (P=0,009). Thus, it can suggested that allopurinol is potent to be use as a remedy to overcome hypertension with hyperuricemia.*

Keywords: *Allopurinol, hypertension, hyperuricemia, endothelin-1, endothelial dysfunction*

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I. Introduction

One of the cardiovascular risk factors and precedes the development of atherosclerosis is endothelial dysfunction. Endothelial dysfunction is a conditions marked by imbalance in the relative contribution of endothelium-derived relaxing and contracting factors including diminished availability of nitric oxide. Nitric oxide (NO) is a vaso-active substances formed by endothelial nitric oxide synthase (NOS). Besides inducing vasodilatation, NO inhibits aggregation of platelets, inhibits adhesion of monocytes and leukocytes to the endothelium [1]. One additional important alteration in endothelial dysfunction is an increased production and biological activity of the potent vasoconstrictor and pro-inflammatory peptide endothelin (ET)-1[2]. The ET family consists of three 21-amino acid peptides i.e. ET-1, ET-2, and ET-3. Among the three peptides, ET-1 is the major vascular isoform and of most importance in the cardiovascular system [3]. Imbalance of vasoconstrictor endothelin (ET) systems, vasodilator nitric oxide (NO), and hyperuricemic condition have been identified as potential contributors to increased cardiovascular risk in patients with chronic kidney disease (CKD) [4]. The linkage of ET, especially ET-1, with various diseases is inevitable because this most potent vasoconstrictor is not only produced by vascular endothelial cells but also by varous cell types including renal tubular endothelium, glomerular mesangium, cardiac myocytes, glia, the pituitary, macrophages, and mast cells [5]. Studies in the past two decades, for examples, have reported associations between elevated serum uric acid levels and cardiovascular events, suggesting a potential role for uric acid as a risk factor for atherosclerosis and related diseases [6]. Scientific reports suggesting a link between hypertension and hyperuricemia are considerable [7]. Clinical trials performed in adolescents with newly diagnosed essential hypertension, for instance, Feig (2012) found that reduction of serum uric acid can reduce blood pressure and suggested that uric acid is likely causative in some cases of early onset hypertension[8]. How uric acid is associated with cardiovascular disease (CVD) is not yet fully understood. There were several authors who argue that hyperuricemia is just a marker, rather than a risk factor of CVD[9].

Among the drugs that commonly used for decades in the management of hyperuricaemia is allopurinol [10]. High-dose (≥300mg) users of allopurinol reached target urate concentration and had significant reduction in the risk of cardiovascular events and mortality [11]. Allopurinol is also revealed by Soletsky et al. (2012) as one among uric acid reducing drugs that effectively cause reduction in blood pressure in pre-hypertensive adolescents [12]. With regard to how allopurinol improve endothelial function, George et al. (2006) suggested that allopurinol has ability to reduce vascular oxidative stress and not in urate reduction [13]. Given endothelin (ET)-1 can be attributed to both hypertension and hyperuricemia, and allopurinol is known as uric acid reducing drugs that effectively cause reduction in blood pressure, then it is worth asking whether allopurinol administration will directly affect changes in concentration of ET-1? To answer the question, a double-blind, placebo-controlled clinical trial using allopurinol has been employed on the hypertensive patients with asymptomatic hyperuricemia hospitalized at Moehammad Hoesin Hospital, Palembang, Indonesia.

II. Materials And Methods

2.1 Patients

Inclusion criteria of the study were patients diagnosed hypertensive with asymptomatic hyperuricemia, aged 18 – 60 years, willing to sign informed consent and enroll in the study. Baseline demographic, hemodynamic and laboratory cahractericticts of all participants were recorded. Demographic characteristics include age, sex, education, occupation, and body mass index (BMI), whereas hemodynamic characteristics include systolic pressure, diastolic pressure, hypertension history, and hyperuricemia history. Baseline laboratory data of the patient were assessed from the patient's blood sample (7 ml in volume) after the patients are fasted for 10-12 hours. The humoral characteristics include hemoglobin, leukocytes, erythrocyte sedimentation rate, platelets, BSS, SGOT, SGPT, ureum, creatinine, total cholesterol, HDL, LDL, triglycerides, and uric acid.

2.2 Study Design

By applying consecutive sampling, a total of 40 patients that fulfilled inclusion criteria, either outpatients or inpatients at the Mohammad Hoesin Hospital, Palembang, Indonesia in the period of December 2016 – May 2017 were designed as research subjects. They consisted of 19 males and 21 females. The participants were separated by double-blind randomization into two groups, the treatments (patients treated with allopurinol) and the placebo. The allopurinol-treated patients included 9 males and 11 females, while placebo consist of 10 males and 10 females. To each patient of both groups were given one capsule per day for one month. For the treatment patients, every capsule given contained allopurinol at the dose of 100 mg.

2.3 Trials and Study Parameters

Of the patients who had been grouped, 5 ml blood was taken for examination of ET-1 levels, uric acid levels, and blood pressure. The results were noted as the before-treatment data. After that capsules contained 100 mg allopurinol were given to the treatment group and those of contained non active substance were given to placebo group once daily. After daily administration of allopurinol or placebo for a month, the patient's blood was taken as much as 5 ml to be measured for ET-1, uric acid, and systolic and diastolic pressure. The results were recorded as after-treatment data. Serum uric acid and ET-1 levels were determined in Prodia Laboratory, Jakarta, Indonesia. Electrochemical techniques were performed for uric acid measurement, whereas ELISA methods were used in ET-1 analysis using human endothelin-1 ELISA Kit from R&D System Minneapolis, USA.

2.4 Data Analyses

The Shapiro-Wilks test for normality were used to assess data distribution regarding characteristics of research subjects. Data with a normal distribution presented as mean (standar deviation), whereas that of with a non-normal distribution peresented as median (minimum-maximum). To compare data between variables, Mann-Whitney comparison test were performed. A p value below 0.05 was considered statistically significant.

III. Results

3.1 Characteristics of the Research Subjects

Characteristics of research subject regarding sex, age, education, occupation, BMI, hypertension and hyperuricemia history are shown in **Table 1**. Demographically, the average age of the patients included in the study is in the working-age category (50.98 ± 8.51 years). It was clearly depicted by the participant occupational data that only 7.5% of the subjects were retired. By educational status, most of the patients are high school graduates (66.5%) or lower, and only 33,5% of them are college graduates. All subjects have been suffered from hypertension for between 1 - 12 years (4 years in average) and hyperuricemia less than 10 years.

Table 1 General Characteristics of Research Subjects			
Characteristics	**Allopurinol**	**Placebo**	**All Subjects**
Sex, n(%)			
Male,	9 (45)	10 (50)	19 (47.5)
Female	11(55)	10 (50)	21 (52.5)
Age, y (mean±SD)	49.85 ± 8.71	52.10 ± 8.37	50.98 ± 8.51
Education, n(%)			
Prymary School	2(10)	1(5)	3 (7.5)
Junior High School	4(20)	2(10)	6 (15)
Senior High School	9(45)	9(45)	18 (45)
Higher Education	5(25)	8(40)	13(33.5)
Occupation, n(%)			
Civil Servants	6(30)	6(30)	12(30)
Private Employees	8(40)	4(20)	12 (30)
Housewife	5(25)	8(40)	13 (32.5)
Retired	1(5)	2(10)	3 (7.5)
BMI, kg/m^2 (mean±SD)	27.8 ± 4.29	26.25 ± 3.73	27.03 ± 4.05
Systolic Pressure, mmHg (min-max)	150 (140-180)	140 (140-170)	150 (140-180)
Diastolic Pressure, mmHg (min-max)	90 (80-100)	90 (80-100)	90 (80-100)
Hypertension, y (min-max)	4 (1-10)	4 (1-12)	4(1-12)
Hyperuricemia, y (min-max)	1.5 (0-8)	1 (0-10)	1 (0-10)

Laboratory characteristics of the research subjects before trials are shown in Table 2. There were no statistical difference regarding every parameters between allopurinol and placebo groups.

Table 2 Laboratory Characteristics of Research Subjects		
Variables	**Allopurinol (mean ± SD)**	**Placebo (mean ± SD)**
Hemoglobin, g/dl	13.04 ± 1.66	12.75 ± 1.68
Leukocyte count	8780 ± 2278	7660 ± 2434
ESR, mm/hr	18.00 (4-88)	29.5 (3-105)
Platelet count	286.35 ± 85.01	266.5 ± 64.72
SGOT, IU/l	26 (13-112)	25.17 (17-89)
SGPT, IU/l	30.30 ± 15.75	26.75 ± 9.64
Urea, mg/dl	28.65 ± 6.83	30.60 ± 6.25
Creatinine, mg/dl	1.11 ± 0.18	1.07 ± 0.13
Total Cholesterol, mg/dl	190.5 ± 58.79	222.5 ± 57.19
HDL, mg/dl	35.75 ± 13.81	36.55 ± 10.56
LDL, mg/dl	121.50 ± 44.49	140.50 ± 49.38
Triglycerides, mg/dl	144 (86-634)	164.5 (114-433)
Uric acid, mg/dl	8.24 ± 1.17	7.743 ± 1.04
Values followed by (min-max) indicate that the data are not distributed normally		

3.2 Characteristics of the Research Variables

Table 3, 4, 5 and 6 are cosecutively depicting effects of allopurinol in comparison with placebo on the concentration of uric acid, systolic pressure, diastolic pressure and endothelin (ET)-1 levels of the research subjects. Referring the data it can be summarized that allopurinol effectively lowers ET-1 level (P = 0.009), systolic pressure (P = 0,013), diastolic pressure (P = 0.012) and uric acid levels (P < 0.001) in patients diagnosed hypertension with hyperuricemia.

Table 3 Comparison of systolic pressure between trials groups before and after treatment				
Trials Group	Systolic Pressure (mmHg)			*P*
	Pre-treatment	Post-treatment	Changes*	
Allopurinol	150 (140-180)	150 (130-170)	10 (-10-20)	0.013
Plasebo	150 (140-170)	150 (140-160)	0 (-10-10)	
P value indicates level of significant differences between parameters marked with (*)				

Table 4 Comparison of diastolic pressure between trials groups before and after treatment				
Trials Group	Diastolic Pressure (mmHg)			*P*
	Pre-treatment	Post-treatment	Changes*	
Allopurinol	90 (80-100)	90 (80-90)	5 (0 - 10)	0,012
Plasebo	90 (80-100)	90 (80-100)	0 (-10 - 10)	
P value indicates level of significant differences between parameters marked with (*)				

Table 5 Comparison of uric acid concentration between trials groups before and after treatment

Trials Group	Concentration of Uric Acid (mg/dl)			*P*
	Pre-treatment	Post-treatment	Changes*	
Allopurinol	8.24 ± 1.169	6.26 ± 1.300	1.98 ± 1.262	0.000
Plasebo	7.743 ± 1.041	7.92 ± 1.174	0.49 ± 1.040	
P value indicates level of significant differences between parameters marked with (*)				

Table 6 Comparison of Endothelin (ET)-1 levels between trials groups before and after treatment

Trials Group	Concentration of ET-1 (pg/ml)			*P*
	Pre-treatment	Post-treatment	Changes*	
Allopurinol	2.09 ± 0.990	1.61 ± 0.586	0.476 ± 0.604	0.009
Placebo	1.51 ± 0.285	1.46 ± 0.385	0.047 ± 0.337	
P value indicates level of significant differences between parameters marked with (*)				

IV. Discussion

Demographic data of this research subjects showed no significant difference in the proportion of male and female sex between allopurinol and placebo groups. Average age of the study subjects was 50,98 ± 8,511 years. Those patients characteristics confirmed what were generally known that the peak incidence of hypertension and hyperuricemia occurred in the age 50-65 years [14]. Within that age range, various metabolic functions have begun to decline. Within that age range, various metabolic functions have begun to decline. In women entering menopause there is a decrease in estrogen hormone that causes decreased in urine urate that might lead to increased risk of hypertension and hyreuricemia[15]. In addition, increased risks of metabolic syndrome, hypertension, kidney function impairment also common in patients within this range of age[16]. With regard to the patients education, our findings differed from other previous studies, also conducted in Palembang, that hypertension patients with hyperuricemia are dominated by those who had college education [17,18]. People with higher education, well-established jobs and good nutrition, tend to have metabolic syndrome, hypertension and hyperuricemia 2.5 times higher than those with lower education [19]. The study findings regarding body mass index, systolic pressure, diastolic pressure and uric acid level seem to meet other previous study reported by Obineche et al. (2010) and Demarco et al.(2011).[20,21].

Our research results clearly show that in hypertensive patients with hyperuricemia. allopurinol significantly lowers both systolic (Table 3) and diastolic (Table 4) pressures. These findings seem to comfirm what were suggested by Agarwal et al. (2013) that allopurinol and other xanthine oxidase inhibitors may be used as adjunctive antihypertensive agent[22]. Unfortunately, Pedro et al. (2013) doubted the claim because many of the studies cited are having methodological defects due to lack of sample and do not apply placebo-controlled trials[23]. . In current study, however, such methodological weaknesses have been overcome by applying more scientific clinical trial principles. As shown in Table 5, research participants treated with allopurinol significantly having lower uric acid levels. This finding seems to confirm why allopurinol has long been used widely to treat gout disease[24]. Allopurinol has been known as inhibitor of xanthine oxidase, an enzyme responsible for uric acid synthesis [25]. Inhibition of xanthine oxidase activity causes excessive formation of uric acid and its deposition in joints decreased [26]. There are many studies that show the linkage of cardiovascular diseases with arterial endothelin (ET)-1 expression. ET-1 plays an important role in atherosclerosis, for which hypertension is an important risk factor, and in ischemic heart disease and stroke. Thus, ET-1 may participate in vascular damage in cardiovascular disease and in blood pressure elevation in experimental models and in human hypertension[27]. Our data, as can be seen in Table 6, clearly showed significant effects of allopurinol administration on the decrease of ET-1 levels in hypertensive patients with hyperuricemia. According to Li et al. (2003), ET-1 affects hypertension by activating NADPH oxidase and superoxide generation [28]. Allopurinol, on the other hand, is known as the xanthine oxidase inhibitor and has proven to show multitude of beneficial effects in the treatment of diabetic cardiomyopathy both in experimental animal models and human [29].

V. Conclusion

In summary, the study revealed that allopurinol effectively reduced levels of ET-1, blood pressure, and uric acid levels in the study subjects. Although the decrease in ET-1 expression is not automatically attributable to allopurinol, the decrease in blood pressure in allopurinol-treated patients shows that allopurinol is efficacious in overcoming endothelial dysfunction. By significantly lowers concentration of uric acid, it is worth to suggest that allopurinol is potent to be use as a remedy to overcome hypertension with hyperuricemia.

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