

Allopurinol as a Preventive Contrivance after Acute Ischemic Stroke in Patients with a High Level of Serum Uric Acid: A Randomized, Controlled Trial

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Key Words

Acute ischemic stroke · Allopurinol · Xanthine oxidase inhibitor · High serum level of uric acid · Modified Rankin scale · Functional outcome · Survival

Abstract

Objectives: To assess the clinical relevance (functional outcome) of a 3-month allopurinol regimen in patients with high serum uric acid (SUA) levels and acute ischemic stroke without considering the changes in SUA levels. **Materials and Methods:** In a randomized, double-blind, controlled study, 70 patients (45 females, 25 males) with acute ischemic stroke who had elevated levels of SUA were included. They were divided in two 35-patient groups to investigate the effect of 3 months of an allopurinol (200 mg/day) regimen versus placebo on their functional outcome, which was evaluated using a modified Rankin scale. **Results:** The overall mean age was 68.9 ± 11.33 years (range 27–89). The final favorable functional status (mRS = 0–2) was 23 (65.7%) and 14 (40.0%) in the treated and placebo groups, respectively, which was strongly associated with allopurinol consumption (OR = 4.646, $p = 0.014$) and age ≤ 70 years (OR = 0.139, $p = 0.005$) in patients with ischemic stroke after adjusting for confounders. There was no significant difference in death between allopurinol-treated cases (3; 8.6%) and placebo-

treated ones (6; 17.2%; $p = 0.278$). **Conclusion:** Allopurinol treatment was well tolerated and improved the 3-month functional status of patients with acute ischemic stroke who had high levels of SUA without considering the decreasing effect of allopurinol on SUA.

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Introduction

Stroke-related morbidity and mortality is one of the main public health concerns, representing the main cause of long-term disability in the adult population, widespread implementation of effective preventative therapy notwithstanding [1–3]. Moreover, the treatment options for patients with acute stroke are limited. Accordingly, identification of new therapeutic approaches and treatments to ameliorate the long-term outcomes of this high-risk population are required. Some investigations have demonstrated that ischemia due to ischemic stroke increases the activity of the xanthine oxidase (XO) enzyme, and this activity is a major source of production of free radicals during ischemia/reperfusion injury [4, 5]. Thus

This clinical trial conforms to the Consort Statement (IRCT ID: IRCT201204299334N1).

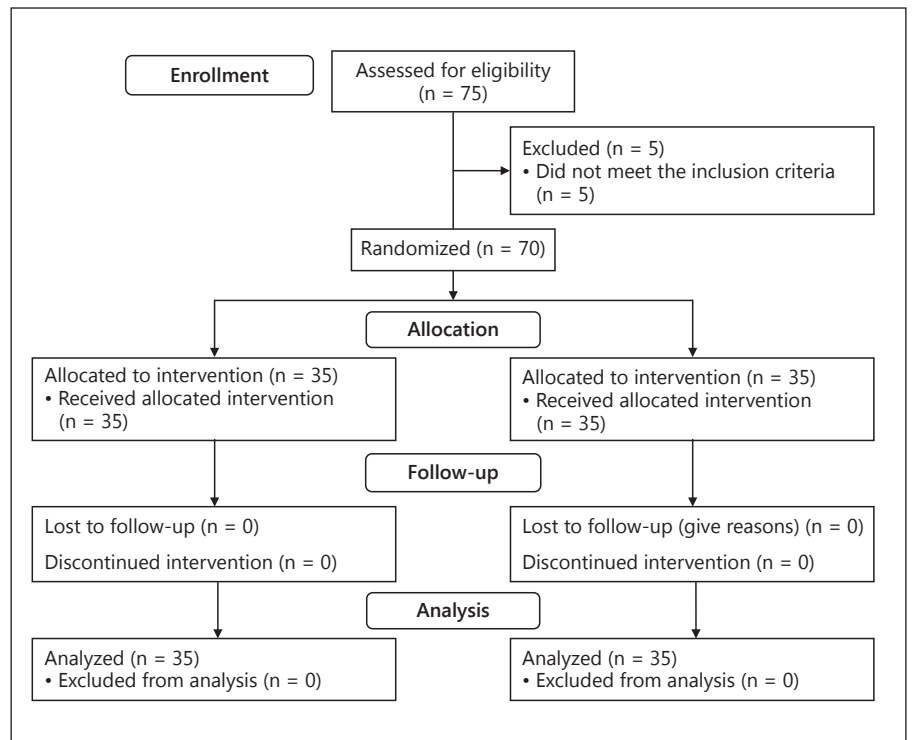


Fig. 1. Randomization and patient flow-chart.

treatment with XO inhibitors (XOI) such as allopurinol may be a potential adjunctive preventive strategy. Besides, XOI inhibit uric acid (UA) production and can reduce serum UA (SUA) levels [6]. However, there is no general agreement on whether or not high SUA improves the prognosis of ischemic strokes [1, 2, 7–12]. XOI may also have supplementary action, such as oxidative stress reduction in the vasculature [13], thereby improving endothelial and peripheral vascular function [14] and reducing the expression of proinflammatory molecules [15]. Therefore, these drugs appear to hold promise for the prevention of adverse events in the acute phase of stroke. Hence the objective of this study was to assess the XO inhibitory effect (other than SUA depletion) of 90-day allopurinol consumption on improvement of the final functional outcome of patients with high SUA levels who had acute ischemic stroke.

Materials and Methods

A prospective randomized, double-blind, placebo-controlled study was carried out at the Division of Neurology of Imam Reza Hospital (an educational and health centre) of the Tabriz University of Medical Sciences from January 2009 to October 2011. Seventy patients, i.e. 45 women and 25 men aged 27–89 years who were diagnosed with acute ischemic stroke during admission, were in-

cluded in this study. Inclusion criteria were: patients with high SUA levels (>6.5 mg/dl for females and >8.2 mg/dl for males) who did not receive thrombolytic agents or investigational drugs and were admitted within the first 24 h of symptom initiation. Exclusion criteria were: severe poststroke disability [National Institutes of Health Stroke Scale (NIHSS) >20] (3 patients); significant comorbidity such as chronic disease of the liver or kidney, or hematologic disease and cancers, or frailty likely to cause death within 3 months; probability to make adherence to the study protocol difficult for patients; a previously documented adverse reaction to allopurinol; a serum creatinine concentration >2.2 mg/dl; gout symptoms; a positive history of recent treatment with allopurinol; strokes secondary to spontaneous brain hemorrhage, trauma, neoplasm, coagulation disorders, aneurysms or arteriovenous malformations, and a positive history of regular consumption of iron or antioxidant vitamins during the 4 weeks preceding study involvement. Blood samples of all study participants were taken during the first day of admission and their SUA was measured by standard laboratory procedures in the Department of Biochemistry. Non-fasting blood samples were collected and centrifuged within 30 min of collection for 15 min at 3,000 rotations/min at room temperature. Subsequently, a Kone Diagnostica reagent kit and a Kone autoanalyzer were used for determination of the SUA activity. All patients signed a written informed consent form, and the study was approved by the Ethics Committee of the Tabriz University of Medical Sciences and was conducted in accordance with the Declaration of Helsinki. Patients were randomly divided into 2 groups (fig. 1) on a 1:1 basis to receive either low-dose (200 mg once daily) allopurinol (case group) or placebo (control group). Randomization of patients was performed by an allocation sequence based on a block size of 5, generated with a computer random number generator.

Table 1. Comparison of demographic and baseline variables

Characteristics	Allopurinol (cases)	Placebo (controls)
Total	35 (50)	35 (50)
Gender		
Male	14 (40.0)	11 (31.4)
Female	21 (60.0)	24 (68.6)
Age, years	70.97±12.89	66.97±10.12
Vascular risk factors		
Diabetes	25 (71.4)	19 (54.3)
Hypertension	14 (40.0)	11 (31.4)
Dyslipidemia	6 (17.1)	7 (20.0)
Cigarette smoking	2 (5.7)	8 (22.9)
Ischemic heart disease	11 (31.4)	9 (25.7)
Myocardial infarction	4 (11.4)	5 (14.3)
Nonfasting blood sugar, mg/dl	174.60±14.82 ^a	150.31±12.25 ^a
Stroke subtype		
Lacunar	12 (34.2)	11 (31.4)
Cardioembolic	8 (22.8)	7 (20.0)
Atherothrombotic	12 (34.2)	14 (40)
Undetermined	3 (8.5)	3 (8.5)
Antidiabetic treatment		
Insulin	12 (34.2)	10 (28.7)
Oral agents	13 (37.1)	9 (25.7)
Drugs that affect vascular function		
ACE inhibitors	35 (100)	35 (100)
Statins		
Baseline functional status (initial mRS score)		
2	4 (11.4)	4 (11.4)
3	21 (60.0)	17 (48.6)
4	10 (28.6)	14 (40.4)
Baseline NIHSS score	11.9±2.3	12.5±2.0
Cholesterol, mg/dl	197.60±42.56	193.26±73.98
Triglycerides, mg/dl	170.89±19.71 ^a	158.59±10.81 ^a
Baseline uric acid, mg/dl	8.46±1.01	8.70±2.99
Creatinine, mg/dl	0.94±0.30	1.01±0.34
Hb, mg/dl	13.70±2.16	13.96±1.63
WBC, ×1,000	9.77±5.09	8.47±2.96
Platelets, ×1,000	218.82±67.52	226.51±45.91
Urea, mg/dl	41.57±18.53	39.89±14.51
Na, mEq/dl	141.77±3.43	144.09±3.02
K, mEq/dl	4.43±0.03	4.39±0.32
ESR, mm in the 1st hour	32.01±25.24	29.28±14.76
HCT, %	43.10±6.8	41.20±6.2
Mean follow-up duration, days	82.91±3.74 ^a	87.51±2.48 ^a

Values are presented as means ± SD or n (%). K = Potassium; Na = sodium; ESR = erythrocyte sedimentation rate; WBC = white blood cells; HCT = hematocrit; Hb = hemoglobin; ACE = angiotensin-converting enzyme.

^a Values are means ± SE.

Allocation was concealed by use of sequentially numbered black envelopes. Dosing began on the first day (after baseline assessment) and continued for 90 days, at which point the participants returned for further assessment of their functional status. Allopurinol tablets were manufactured by Jalinous Pharmaceutical Company, Tehran, Iran. Demographics, baseline risk factors, characteristics of patients, main workup findings, in-hospital events, primary modified Rankin scale (mRS) and NIHSS, as well as therapies administered before and during hospitalization were collected by stroke neurologists. Neurological impairment was measured at baseline and at hospital discharge using an mRS (normal = 0 to death = 6). All drug treatments remained unchanged throughout the study period. The schedule of the placebo-controlled study was assessed via questioning and pill counts during follow-up in both groups. All patients received the standard protocol of care ordered by an expert stroke care team. This study was considered double blind, meaning that the patients, all care unit staff and investigators were not informed of classification or assignment. All patients, excluding 9 who died, completed their clinical 90-day follow-up. A standard protocol was used for the evaluation of all patients. As our primary end point, the outcomes of cases and controls (considering final SUA levels and SUA level depletion) using functional status (mRS) and mortality rates were compared. mRS scores of 0–2 were classified as a favorable functional status, and scores of 3–6 were categorized as an unfavorable functional status including mortality. Secondly, the effect of low-dose consumption of allopurinol on final favorable functional status in the presence of high SUA levels in patients with acute ischemic stroke was evaluated.

Statistical Analysis

It was calculated that a sample size of 29 patients per group would enable the detection of a clinically meaningful 30% change in mRS following allopurinol treatment with more than 80% power ($\alpha = 5\%$, assumed SD = 10%). However, in order to guarantee a 10–15% dropout rate and further losses due to mortality and follow-up, 70 patients were recruited. Univariate analyses to compare the effect of allopurinol consumption on the final mRS between the two groups of patients were done. To highlight the XO inhibitory effect (other than its effect on SUA depletion) of allopurinol on favorable functional status (mRS = 0–2) in the case group, a multivariable stepwise logistic regression model adjusted for confounders was constructed and the associations are presented as OR with 95% CI. Model discrimination was measured using the c statistic, which is equal to the area under the receiver operating characteristic (ROC) curve. Model calibration was estimated using the Hosmer-Lemeshow (HL) goodness-of-fit statistic (higher p values imply that the model fits the observed data better). For statistical analysis, the statistical software SPSS version 13.0 for Windows (SPSS Inc., Chicago, Ill., USA) was used. All p values were 2-tailed, and $p < 0.05$ was considered statistically significant.

Results

The mean baseline NIHSS score was 12.21 ± 2.1 . The comparison of demographic and baseline variables including laboratory findings, baseline UA and mRS is listed in table 1. There were no significant differences be-

tween the two groups in terms of basic characteristics (table 1), follow-up time, baseline functional status ($p = 0.657$) and baseline SUA ($p = 0.663$; all p values were >0.05). The final SUA level was significantly lower ($p = 0.045$) and SUA depletion was significantly lower in the case group ($p = 0.008$); 23 (65.7%) of the allopurinol-treated patients had final favorable functional status (mRS = 0–2) in comparison to 14 (40%) placebo-treated patients ($p = 0.031$). The mortality rate was 3 (8.6%) in cases and 6 (17.1%) in placebo-treated patients; the difference was not statistically significant ($p = 0.278$). Predictive factors associated with final favorable functional status by univariate analysis are given in table 2. Data showed that age ($p = 0.001$), allopurinol consumption ($p = 0.031$), baseline mRS (<0.001) and final SUA level (0.028) were significantly associated with favorable functional status (mRS = 0–2). After adjusting for the confounding effects of baseline mRS, final SUA level and SUA level depletion, final favorable functional status was significantly associated with allopurinol consumption (OR = 4.646, $p = 0.014$) and age ≤ 70 years (OR = 0.139, $p = 0.005$) (HL goodness of fit test, $p = 0.717$; area under the ROC curve, $c = 0.631$). The distribution of mRS scores in the treated and control groups is displayed in figure 2. The main adverse events were skin rashes, transient digestive disorders (nausea, diarrhea and abdominal pain), hepatic enzyme disorders, drowsiness, paresthesia and headache. Skin rashes and transient digestive disorders were more frequent in the allopurinol group, but no serious adverse event was observed (table 3).

Discussion

Allopurinol-treated patients had a higher rate of final favorable functional status compared to placebo patients, but there were no significant differences in mortality rate between the two groups. The study of McCord [16] showed that allopurinol acts like a free-radical inhibitor and prevents tissue damage during ischemia and reperfusion. Betz [17] demonstrated that XO activity in an isolated ischemic area of brain was 4 times higher than has been reported elsewhere. Martz et al. [18] showed that administration of allopurinol in a rat model reduced cerebral infarct size after middle cerebral artery occlusion. Marro et al. [19] in their study on pigs showed that administration of allopurinol inhibits hypoxia and brain cell damage. In their research, SUA levels and brain receptors in the allopurinol group were significantly lower than in the control group [19]. Akdemir et al. [20] evaluated the

Table 2. Predictive factors associated with final favorable functional status by univariate analysis

Characteristics	Final favorable functional status (mRS = 0–2)	Final unfavorable functional status (mRS = 3–6)	p value
Total	37 (52.9)	33 (47.1)	
Gender			0.164
Male	16 (43.2)	9 (27.3)	
Female	21 (56.8)	24 (72.7)	
Age			0.004
≤ 70 years	26 (70.3)	12 (36.4)	
> 71 years	11 (29.7)	21 (63.6)	
Vascular risk factors			
Diabetes	23 (62.2)	21 (63.6)	0.899
Hypertension	11 (29.7)	14 (42.4)	0.269
Dyslipidemia	8 (21.6)	5 (15.2)	0.487
Cigarette smoking	2 (5.4)	8 (24.2)	0.025
Ischemic heart disease	8 (21.6)	12 (36.4)	0.173
Myocardial infarction	5 (13.5)	4 (12.1)	0.862
Groups			0.031
Placebo-treated patients (controls)	14 (37.8)	21 (63.3)	
Allopurinol-treated patients (cases)	23 (62.2)	12 (36.4)	
Functional status (baseline mRS score)			0.011
2	7 (18.9)	1 (3.0)	
3	25 (67.6)	13 (39.4)	
4	5 (13.5)	19 (57.6)	
White blood cells, $\times 1,000$	9.00 \pm 3.49	9.25 \pm 4.90	0.806
Platelets, $\times 1,000$	224.00 \pm 66.81	221.18 \pm 45.71	0.839
Initial UA, mg/dl	8.35 \pm 1.27	8.84 \pm 2.94	0.365
Final UA, mg/dl	7.65 \pm 1.14	8.65 \pm 2.43	0.028
SUA depletion	0.70 \pm 1.24	0.18 \pm 0.82	0.048

Values are presented as means \pm SD or n (%).

Table 3. Adverse events in the groups

Event	Intervention group	Control group
Skin rashes or dermatitis	4 (11.4%)	0
Nausea	6 (17.1%)	5 (14.2%)
Abdominal pain	4 (11.4%)	2 (5.7%)
Diarrhea	4 (11.4%)	3 (8.5%)
Hepatic enzyme disorders	2 (5.7%)	1 (2.8%)
Drowsiness	4 (11.4%)	5 (14.2%)
Paresthesia	1 (2.8%)	1 (2.8%)
Headache	7 (20%)	9 (25.7%)

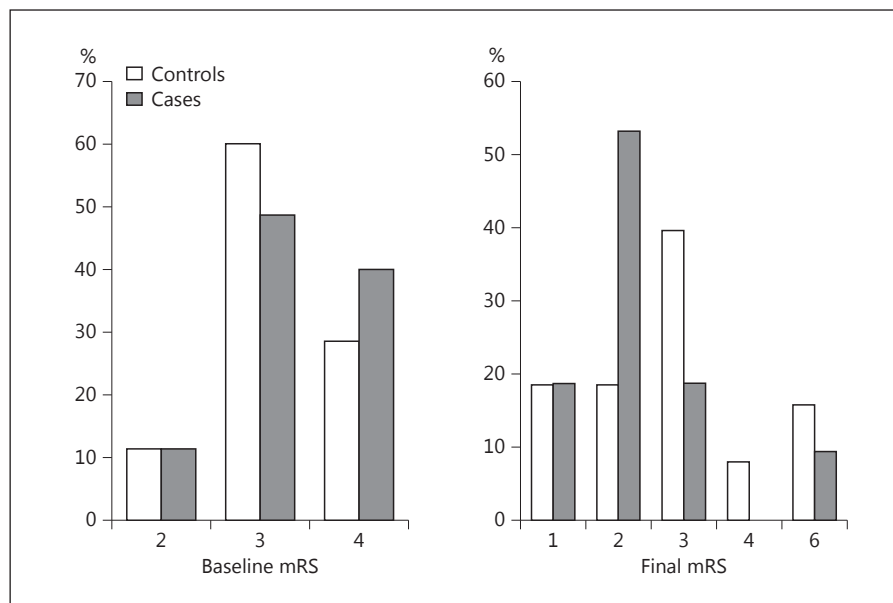


Fig. 2. Distribution of mRS scores in the treated and control groups.

effects of 150 mg/kg of allopurinol administration prior to cerebral ischemia in a rabbit model through middle cerebral artery occlusion. They demonstrated that early nerve injury and delayed brain damage, especially in the perifocal area, were significantly lower in the intervention group than in the control group [20]. Khan et al. [21] assessed the effect of oral consumption of 300 mg allopurinol daily for about 8 weeks on cerebral artery function by using arterial wave reflection in 30 patients with ischemic stroke and high levels of SUA. Accordingly, their study revealed that cerebrovascular function was significantly better in the allopurinol-treated group compared to the controls [21]. However, some studies were not in agreement with these findings. Muir et al. [22] in another study evaluated the effect of high-dose (300 mg/day) and low-dose (100 mg/day) allopurinol for 6 weeks after ischemic stroke. Patients were evaluated 7 days and 6 weeks after their stroke and it was demonstrated that the brain inflammatory factors in the intervention group were significantly lower. However, no significant difference in neurological recovery was noted between the groups [22]. In the work of Sánchez-Moreno et al. [23], ischemic stroke patients were treated with an oral dose of 300 mg of allopurinol/placebo once daily and SUA levels within these groups were compared. It was found that the SUA levels were not considerably lower in the intervention group compared to the control group after treatment [23]. Dawson et al. [24] in a randomized, double-blind, controlled study investigated the effect of a 3-month

course of 300 mg allopurinol once daily versus placebo on cerebrovascular reactivity in individuals with recent subcortical stroke (between 2 weeks and 6 months after acute stroke). They assessed mean flow velocity in the internal carotid artery and middle cerebral artery, but they found no benefit in their study [24]. In this investigation, to determine either the dose of allopurinol consumption or whether SUA reduction improves final functional status, we first determined the predictive factors associated with final favorable functional status (mRS = 0–2) by univariate analysis. The current study demonstrated that age ≤ 70 years, allopurinol consumption, baseline mRS score, final SUA level and SUA depletion were associated with final favorable functional status. Elevated SUA levels were associated with the development of subclinical atherosclerosis [25]. Brouns et al. [26] demonstrated that decreases in SUA during the first week after the onset of stroke correlate with a more severe stroke, unfavorable stroke evolution and poor long-term stroke outcomes [26]. Seet et al. [27] revealed no significant relationship between SUA and vascular outcomes and found that, depending on the SUA level, it may exhibit protective and deleterious effects on stroke outcomes [27]. Weir et al. [2] showed that higher SUA levels cause poor outcomes and higher vascular event rates [2]. In our study, after adjusting for confounders by logistic regression analysis, we found that age ≤ 70 years and allopurinol consumption are associated with final favorable functional status (mRS = 0–2), and there was no association between the final SUA level and

SUA depletion and final favorable functional status. This result was in accordance with the study of George et al. [28] which revealed that SUA reduction is not a mechanism of beneficial effects of allopurinol in chronic heart failure patients treated with allopurinol [28].

This study had a number of limitations including: the small number of patients; that the treatment was stopped after 3 months, which did not allow long-term prognosis, and that a potential random error could not be eliminated completely.

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Conclusion

Administration of allopurinol in patients with acute ischemic stroke, who had high levels of SUA, significantly increased the rate of favorable functional status without a decrease in the mortality rate, and it was well tolerated by patients. Therefore, this drug might help acute ischemic patients with high SUA levels if administered at the time of acute events.