Int J Clin Exp Med 2018;11(3):1390-1400
www.ijcem.com /ISSN:1940-5901/IJCEM0060858

Review Article

Allopurinol to influence blood pressure in hypertension patients: systematic review and meta-analysis

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Received April 14, 2017; Accepted December 31, 2017; Epub March 15, 2018; Published March 30, 2018

Abstract: The increase of serum uric acid (UA) is considered to be associated with the development and progress of hypertension, and the influence of allopurinol, a UA-lowering agent, on patients with hypertension is still unclear. This study aimed to sysmatically evaluate the influence of allopurinol on the blood pressure (BP) in patients with hypertension as well as its safety. Computer retrieval of PubMed, EMbase and Cochrane library as well as WEB SCINENCE was performed for randomized controlled trials (RCTs) pertinent to the effect of allopurinol on the BP of patients with hypertension, with no language restraint for the studies. The changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were used as the primary endpoints, and the changes in serum UA and the incidence of adverse reactions as the secondary endpoints. A total of six RCTs along with 419 patients were included, with a follow-up of 6.67±3.27 weeks. Compared with the control group, a significant decrease was observed in allopurinol group in SBP (mean difference [MD] = 5.42, 95% confidence interval [CI] = 3.99-6.85, P < 0.001), DBP [MD = 4.07, 95% CI = -2.84-5.30, P < 0.001) and serum uric acid (MD = 2.05, 95% CI = 1.32-2.78, P < 0.001). Subgroup analysis also revealed a remarkably lowered SBP and DBP in adults (> 18 years) and adolescents (< 18 years) of allopurinol group in relative to the control group. Low-(≤ 300 mg/d) or high-(> 300 mg/d) dose allopurinol were associated with a significant reduction in SBP. Low-dose allopurinol (< 300 mg/day) was more effective at reducing DBP than high-dose (> 300 mg/day). Indeed, allopurinol can lower the BP in patients with hypertension.

Keywords: Hypertension, allopurinol, serum uric acid

Introduction

As a most commonly seen chronic disease in the world [1], hypertension is the most important pathogenesis leading to cardio-cerebrovascular diseases, kidney diseases and death [2, 3]. Uric acid (UA) produced as a final product from purine metabolism, catalysis by xanthine oxidoreductase [4]. In addition to the association of elevated UA with gout, evidence suggests that elevated UA is associated with hypertension [5], cardiovascular disease [6] and renal disease [7, 8], even potentially acts as an intermediate causing hypertension [9]. Studies show that the relative risk rate for hypertension elevated by 13% with every 3.5 mg/dL of increase in the level of serum uric acid with traditional risk factors for hypertension adjusted [10]. Hyperuricemia is detected in 25%-40% of the untreated patients with primary hypertension as well as in 89% of newly diagnosed youth patients with essential hypertension [11-13].

Although evidence shows that elevated UA is associated with the development and progression of these diseases, it remains unclear if UA-lowering therapy reduce the risk associated with elevated UA levels. Allopurinol as a xanthine oxidase inhibitor [14], used to reduce the level of serum UA in patients with gout. Although some studies report that allopurinol can also lower the blood pressure (BP) in addition to decreasing the level of serum UA, the opposite results are obtained by other researchers [15-17]. Disputes also exist in previously conducted review and meta-analysis concerning the potential antihypertensive effect of allopurinol [18, 19]. Moreover, the specific mechanism of allopurinol effect on BP also re-

mains unclear, if it can be attributed to allopurinol itself or a decrease in UA level.

Therefore, in the present study, an exploration was made to clarify the antihypertensive effect of allopurinol on patients with hypertension.

Materials and methods

Study selection

Inclusion criteria: 1) Randomized controlled trials (RCTs) involving with the effect of allopurinol on the BP of patients with hypertension, with or without blind method or allocation concealment employed; 2) BP assessed at office, home or with ambulatory monitor; 3) Comparable baseline characteristics between allopurinol and placebo; 4) Clear description of outcome measures as well as of patient withdrawals and dropouts; 5) Statistical method accurately described; 6) Parallel or crossover trials; 7) Only the data before the washout period used in a crossover test; 8) Available baseline data and changes in BP; 9) With a follow-up of at least 4 weeks; 10) Participants of any gender, age or ethnicity, with adult primary hypertension defined as a systolic BP (SBP) > 140 mmHg and/or diastolic BP (DBP) > 90 mmHg. Adolescent essential hypertension with confirmed stage 1 hypertension (BP > 95th percentile for sex, age, and height percentile; 11) Participants without using or changing any antihypertensive drug except for allopurinol. Exclusion criteria: 1) Studies on secondary hypertension were excluded; 2) Only the abstract reported for reference; 3) Studies with duplicated data, including same group of patients or for whom there were updated results available; 4) The study have no interest outcomes; 5) The study have no quantitative outcomes; 6) Animal test and review; 7) Malignant hypertension or white coat hypertension; 8) The study populations were prehypertension. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Henan University of Science and Technology. Written informed consent was obtained from all participants.

Search strategy

PubMed, EMbase, Cochrane Central Register of Controlled Trials and WEB of SCINENCE were retrieved. Medical subject headings: "Hypertension", "Blood Pressure", "Allopurinol", "Randomized Controlled Trials"; Keywords: "hemodynamic parameters", "antigout agent", "xanthine oxidase inhibitor", "controlled clinical trials", "diastolic pressure", "systolic pressure". Time frame for the retrieval: establishment of the database to February 1, 2017. The reference lists of identified articles and bibliographies of original articles were also reviewed.

Outcome assessed

Primary endpoints: SBP, DBP; Secondary endpoints: changes in the level of serum UA, the incidence of adverse reactions.

Data extraction

Data were independently extracted from each study by two authors (JD Zhao and JJ Jia) and entered onto a structured spreadsheet, followed by a cross check procedure. Disagreements were resolved by consensus or by a third investigator (P. Dong). The following data were extracted from each trial: the first author's surname, year of publication; demographic and methodological data; total number, mean age, gender distribution and race of enrolled patients; the using or changing antihypertensive drug; baseline seated systolic and diastolic BP (SBP and DBP), and serum uric acid (UA) at baseline, when available; number of patients randomized assigned to each intervention; duration of therapy; incidence and type of adverse events; number of dropouts or with drawals because of adverse events; and change from baseline of seated SBP, DBP and UA. Primary endpoints have no loss statistic; Jalalzadeh et al. [24] lack of report about uric acid changes, after consultation and decided to remove this study. Only the study by Segal et al. [26] reported the adverse events, so unable to meta analysis this endpoint, this study describes the adverse events detailed by summarizes the other studies which reported the adverse events related to allopurinol.

Quality assessment

Criteria for RCT bias risk evaluation listed in Cochrane Handbook for Systematic Reviewer 5.0.1 were adopted, including: 1) Random sequence generation, 2) Allocation concealment, 3) Blinding of patients and personnel, 4)

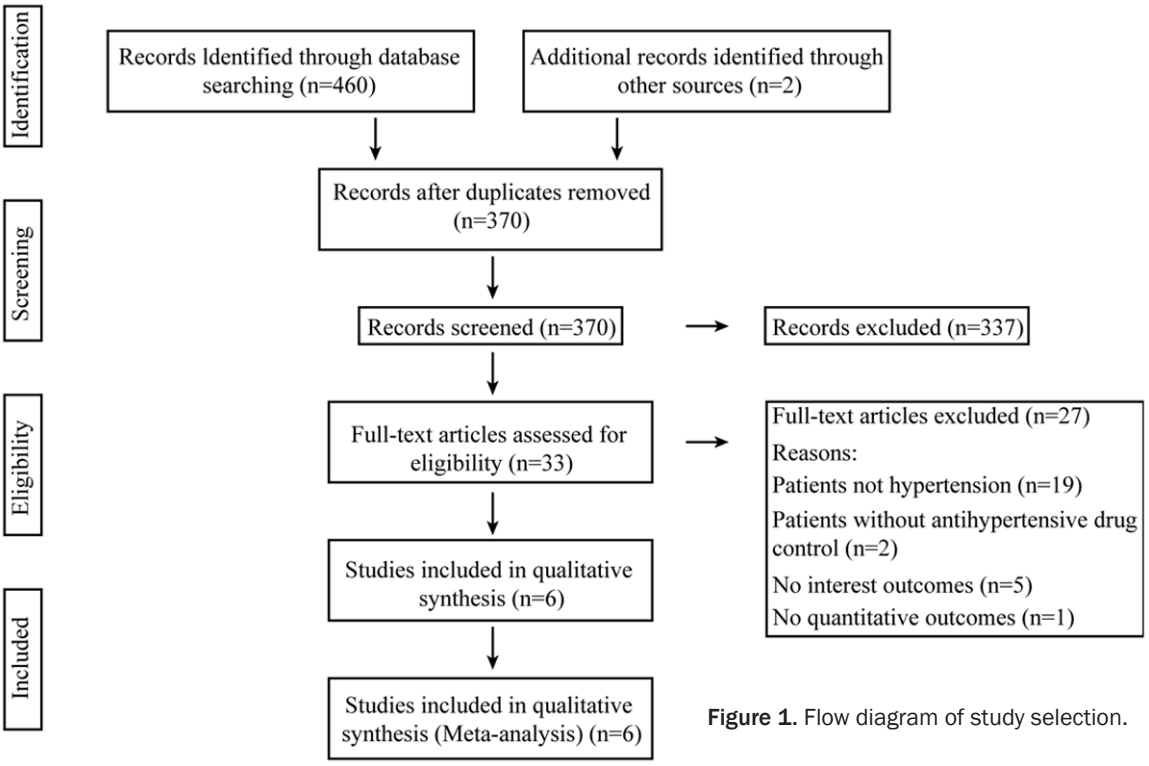


Figure 1. Flow diagram of study selection.

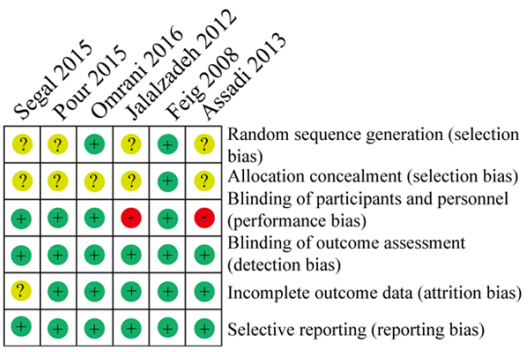


Figure 2. Quality assessment.

Blinding of outcome assessment, 5) Incomplete outcome data, 6) Selective reporting risk. Then an evaluation system with "low risk", "high risk" and "not clear" was established according to the six criteria as describes above [20].

Data analysis and synthesis

RevMan5.0 software was employed for data analysis, with risk ratio (RR) and 95% confidence interval (CI) used for binary variables, mean difference (MD) and 95% CI for continuous variables in curative effect analysis, as well as a test level $\alpha = 0.05$. Following clinical heterogeneity analysis of the included studies, statistical heterogeneity was assessed using X^2 based Cochran Q statistic and I^2 [21]. For the Q statistic, $P \geq 0.1$ indicates homogeneity among multiple similar studies, and fixed effects model can be employed for Meta analysis; while $P < 0.1$ indicates were considered to indicate statistically significant heterogeneity, analyzed by random-effects model. For the I^2 statistic, $I^2 < 25\%$ indicates low heterogeneity, while $I^2 > 50\%$ indicates moderate to high heterogeneity [22].

Results

Selection and description of studies

462 published papers were collected after the initial screening, and eventually six RCTs [13, 23-27] with a total of 419 patients including 225 cases in allopurinol group and 224 cases in the control group were included through reviewing the title, abstract and full text, as well as eliminating duplicate documents, non-randomized controlled trials, and those failed to meet the inclusion criteria. See **Figure 1** for the screening process.

In the six included studies [13, 23-27], only study [13] from Feig reported a correct random

Table 1. Study characteristics

Author	Design	Blinding	Allopurinoldose	Duration	Allopurinol group	Control group	Allopurinol group Dropout (%)	Control group Dropout (%)
Feig et al. 2008 [13]	Cross-over RCT	Double-blind	400 mg/d	4 weeks	Allopurinol	Placebo	0	0
Assadi et al. 2013 [23]	Prospective RCT	Open-label	300 mg/d	8 weeks	Enalapril + Allopurinol	Enalapril	14	17
Jalalzadeh et al. 2012 [24]	Cross-over RCT	Single-blind	100 mg/d	12 weeks	Allopurinol	Blank	0	7
Pour et al. 2015 [25]	Prospective RCT	Double-blind	200 mg/d	8 weeks	Allopurinol	Placebo	0	0
Segal et al. 2015 [26]	Prospective RCT with 2 × 2 factorial design	Double-blind	300 mg/d	4 weeks	Allopurinol	Placebo	19	23
Omrani et al. 2016 [27]	Prospective RCT	Double-blind	100 mg/d	4weeks	Allopurinol	Placebo	0	0

Table 2. Study population characteristics

Author	Intervention	Number	Age (years)	Male (%)	SBP (mmHg)	DBP (mmHg)	SUA (mg/dL)	Weight
Feig et al. 2008 [13]	Allopurinol	30	15.7±5.6[c]	60%[c]	138±10.71	83±8.0	7±1.3	95±29.46[a]
	Placebo	30			138±8.0	82±8.0	6.2±1.9	95.5±33.48[a]
Assadi et al. 2013 [23]	Enalapril + Allopurinol	24	15.5±8.3	60%	132.5±10.7	83.5±8.3	6.7±0.9	60.5±15.39[a]
	Enalapril	20	14.5±5.3	54%	132.5±7.5	84±4.3	6.7±1.3	58.5±5.34[a]
Jalalzadeh et al. 2012 [24]	-Allopurinol	28	55.89±15.79[c]	62%[c]	135.18±27.5	78.88±11.54	7.71±1.53[c]	68.77±14.09[a]
	Blank	25			140.83±28.5	80.83±15.01		57.92±10.14[a]
Pour et al. 2015 [25]	Allopurinol	25	51.84±12.65	48%	144.00±9.35	93.80±2.17	7.22±0.76	NR
	Placebo	25	55.00±11.75	48%	146.00±7.21	89.76±8.83	6.90±0.68	NR
Segal et al. 2015 [26]	Allopurinol	56	50.8±10.1	50%	119.9±13.6	75.9±7.9	6.6±1.4	34.5±7.3[b]
	Placebo	54	51.1 ± 7.7	50%	117±11.2	73.7±8.1	6.8±1.7	34.5±6.8[b]
Omrani et al. 2016 [27]	Allopurinol	62	55±3.7	39%	165.80±12.22	100±6.77	7.51±0.98	NR
	Placebo	70	57±4.5	43%	165.42±10.02	99.14±3.70	7.36±0.86	NR

Note: a: Weight (kg); b: Body mass index (kg/m^2); c: Total test population data; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NR: Not reported.

method with allocation concealment adopted; and double blind was used in 4 studies, single blind in one and open-label in the other study. See **Figure 2** for evaluation on the methodology of the studies.

Data of the curative effect on the BP and Level of UA were reported in all the included studies, with the incidence of adverse reactions mentioned in study [26]. Dropout or withdrawal from the research was covered in all the included studies. The study characteristics are shown in **Table 1**, and the basic information of the include population in **Table 2**.

Effects of allopurinol on SBP

The changes in SBP of the patients were reported in all the six studies [13, 23-27], which showed low levels of heterogeneity among the results of the studies (heterogeneity X^2, P = 0.23, I^2 = 27%), thus supporting the analysis using the fixed effect model. Compared with the control group, a significant decrease was observed in allopurinol group in SBP (mean difference [MD] = 5.42, 95% confidence interval [CI] = 3.99-6.85, P < 0.001) (**Figure 3A**).

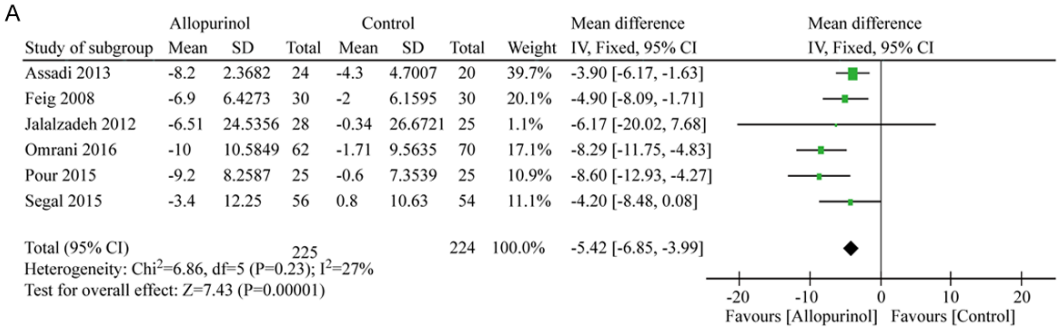
Effects of allopurinol on DBP

The changes in DBP of the patients were reported in all the six studies [13, 23-27], which showed low levels of heterogeneity among the results of the studies (heterogeneity X^2, P = 0.26, I^2 = 23%), thus supporting the analysis using the fixed effect model. Compared with the control group, a significant decrease was observed in allopurinol group in DBP (MD = 4.07, 95% CI = -2.84-5.30, P < 0.001) (**Figure 3B**).

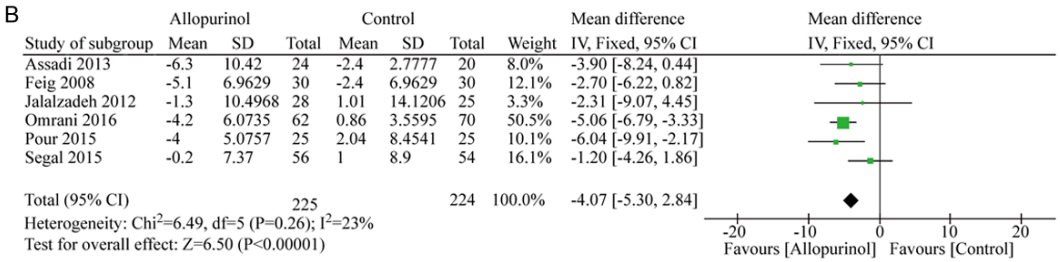
Effect of allopurinol on serum UA

Although the six studies [13, 23-27] recorded the changes in serum UA, only 5 of them [13, 23, 25-27] were considered to meet the requirements for data pooling for Meta analysis as the changes in serum UA was only reported in the allopurinol group in study [24]. The

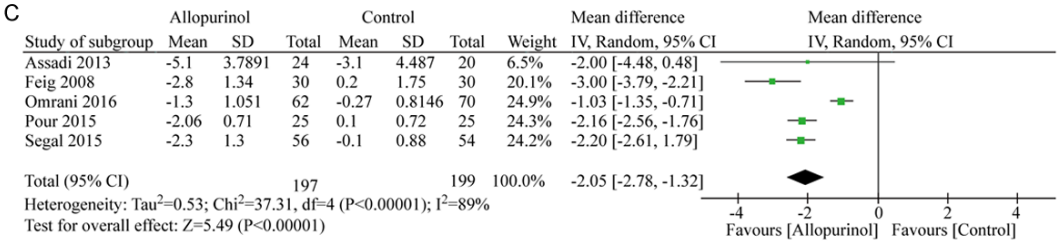
A


Allopurinol
Control
Mean difference
Mean difference
Study of subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Assadi 2013 -8.2 2.3682 24 -4.3 4.7007 20 39.7% -3.90 [-6.17, -1.63]
Feig 2008 -6.9 6.4273 30 -2 6.1595 30 20.1% -4.90 [-8.09, -1.71]
Jalalzadeh 2012 -6.51 24.5356 28 -0.34 26.6721 25 1.1% -6.17 [-20.02, 7.68]
Omrani 2016 -10 10.5849 62 -1.71 9.5635 70 17.1% -8.29 [-11.75, -4.83]
Pour 2015 -9.2 8.2587 25 -0.6 7.3539 25 10.9% -8.60 [-12.93, -4.27]
Segal 2015 -3.4 12.25 56 0.8 10.63 54 11.1% -4.20 [-8.48, 0.08]
Total (95% CI) 225 224 100.0% -5.42 [-6.85, -3.99]
Heterogeneity: Chi²=6.86, df=5 (P=0.23); I²=27%
Test for overall effect: Z=7.43 (P=0.00001)
-20 -10 0 10 20
Favours [Allopurinol] Favours [Control]

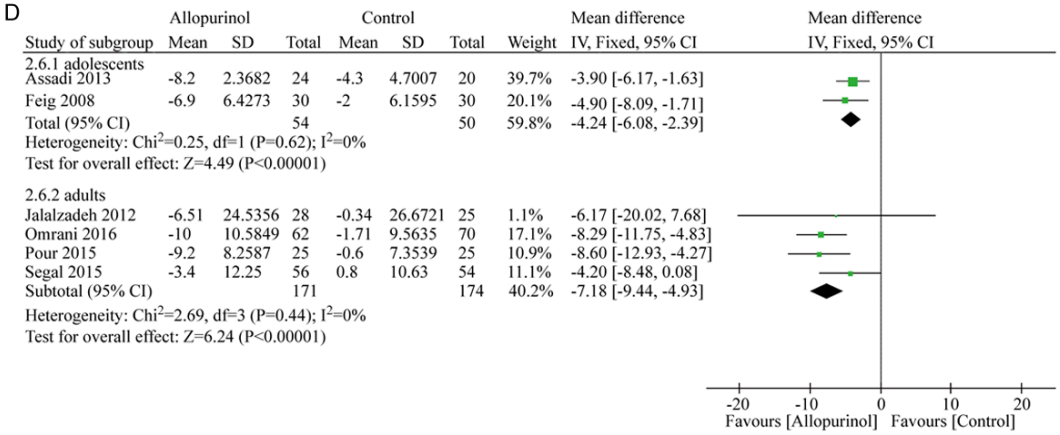
B


Allopurinol
Control
Mean difference
Mean difference
Study of subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Assadi 2013 -6.3 10.42 24 -2.4 2.7777 20 8.0% -3.90 [-8.24, 0.44]
Feig 2008 -5.1 6.9629 30 -2.4 6.9629 30 12.1% -2.70 [-6.22, 0.82]
Jalalzadeh 2012 -1.3 10.4968 28 1.01 14.1206 25 3.3% -2.31 [-9.07, 4.45]
Omrani 2016 -4.2 6.0735 62 0.86 3.5595 70 50.5% -5.06 [-6.79, -3.33]
Pour 2015 -4 5.0757 25 2.04 8.4541 25 10.1% -6.04 [-9.91, -2.17]
Segal 2015 -0.2 7.37 56 1 8.9 54 16.1% -1.20 [-4.26, 1.86]
Total (95% CI) 225 224 100.0% -4.07 [-5.30, 2.84]
Heterogeneity: Chi²=6.49, df=5 (P=0.26); I²=23%
Test for overall effect: Z=6.50 (P<0.00001)
-20 -10 0 10 20
Favours [Allopurinol] Favours [Control]

C


Allopurinol
Control
Mean difference
Mean difference
Study of subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Assadi 2013 -5.1 3.7891 24 -3.1 4.487 20 6.5% -2.00 [-4.48, 0.48]
Feig 2008 -2.8 1.34 30 0.2 1.75 30 20.1% -3.00 [-3.79, -2.21]
Omrani 2016 -1.3 1.051 62 -0.27 0.8146 70 24.9% -1.03 [-1.35, -0.71]
Pour 2015 -2.06 0.71 25 0.1 0.72 25 24.3% -2.16 [-2.56, -1.76]
Segal 2015 -2.3 1.3 56 -0.1 0.88 54 24.2% -2.20 [-2.61, 1.79]
Total (95% CI) 197 199 100.0% -2.05 [-2.78, -1.32]
Heterogeneity: Tau²=0.53; Chi²=37.31, df=4 (P<0.00001); I²=89%
Test for overall effect: Z=5.49 (P<0.00001)
-4 -2 0 2 4
Favours [Allopurinol] Favours [Control]

D


Allopurinol
Control
Mean difference
Mean difference
Study of subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
2.6.1 adolescents
Assadi 2013 -8.2 2.3682 24 -4.3 4.7007 20 39.7% -3.90 [-6.17, -1.63]
Feig 2008 -6.9 6.4273 30 -2 6.1595 30 20.1% -4.90 [-8.09, -1.71]
Total (95% CI) 54 50 59.8% -4.24 [-6.08, -2.39]
Heterogeneity: Chi²=0.25, df=1 (P=0.62); I²=0%
Test for overall effect: Z=4.49 (P<0.00001)
2.6.2 adults
Jalalzadeh 2012 -6.51 24.5356 28 -0.34 26.6721 25 1.1% -6.17 [-20.02, 7.68]
Omrani 2016 -10 10.5849 62 -1.71 9.5635 70 17.1% -8.29 [-11.75, -4.83]
Pour 2015 -9.2 8.2587 25 -0.6 7.3539 25 10.9% -8.60 [-12.93, -4.27]
Segal 2015 -3.4 12.25 56 0.8 10.63 54 11.1% -4.20 [-8.48, 0.08]
Subtotal (95% CI) 171 174 40.2% -7.18 [-9.44, -4.93]
Heterogeneity: Chi²=2.69, df=3 (P=0.44); I²=0%
Test for overall effect: Z=6.24 (P<0.00001)
-20 -10 0 10 20
Favours [Allopurinol] Favours [Control]

E

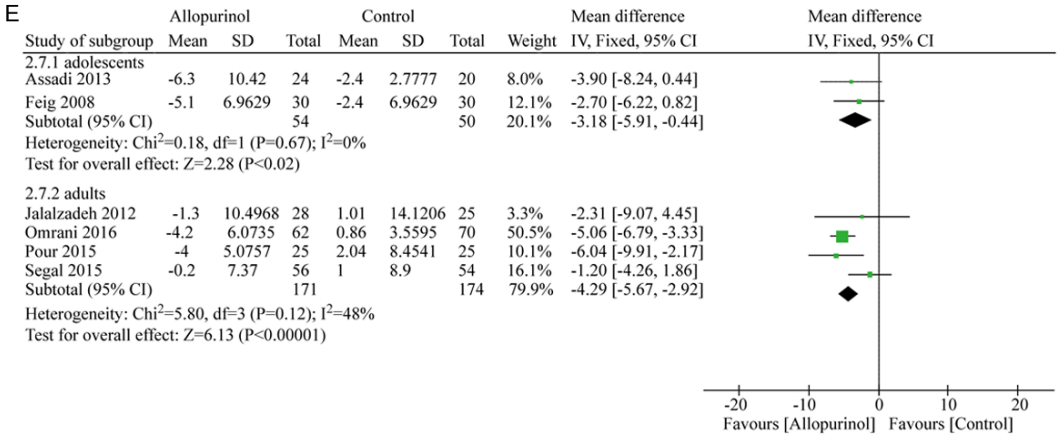

Allopurinol
Control
Mean difference
Mean difference
Study of subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
2.7.1 adolescents
Assadi 2013 -6.3 10.42 24 -2.4 2.7777 20 8.0% -3.90 [-8.24, 0.44]
Feig 2008 -5.1 6.9629 30 -2.4 6.9629 30 12.1% -2.70 [-6.22, 0.82]
Subtotal (95% CI) 54 50 20.1% -3.18 [-5.91, -0.44]
Heterogeneity: Chi²=0.18, df=1 (P=0.67); I²=0%
Test for overall effect: Z=2.28 (P<0.02)
2.7.2 adults
Jalalzadeh 2012 -1.3 10.4968 28 1.01 14.1206 25 3.3% -2.31 [-9.07, 4.45]
Omrani 2016 -4.2 6.0735 62 0.86 3.5595 70 50.5% -5.06 [-6.79, -3.33]
Pour 2015 -4 5.0757 25 2.04 8.4541 25 10.1% -6.04 [-9.91, -2.17]
Segal 2015 -0.2 7.37 56 1 8.9 54 16.1% -1.20 [-4.26, 1.86]
Subtotal (95% CI) 171 174 79.9% -4.29 [-5.67, -2.92]
Heterogeneity: Chi²=5.80, df=3 (P=0.12); I²=48%
Test for overall effect: Z=6.13 (P<0.00001)
-20 -10 0 10 20
Favours [Allopurinol] Favours [Control]

Figure 3. A: Forest plot showing the effect of allopurinol on systolic blood pressure; B: Forest plot showing the effect of allopurinol on diastolic blood pressure; C: Forest plot showing the effect of allopurinol on serum uric acid; D: Subgroup analysis of effect of allopurinol on systolic blood pressure according to patients' age; E: Subgroup analysis of effect of allopurinol on diastolic blood pressure according to patients' age.

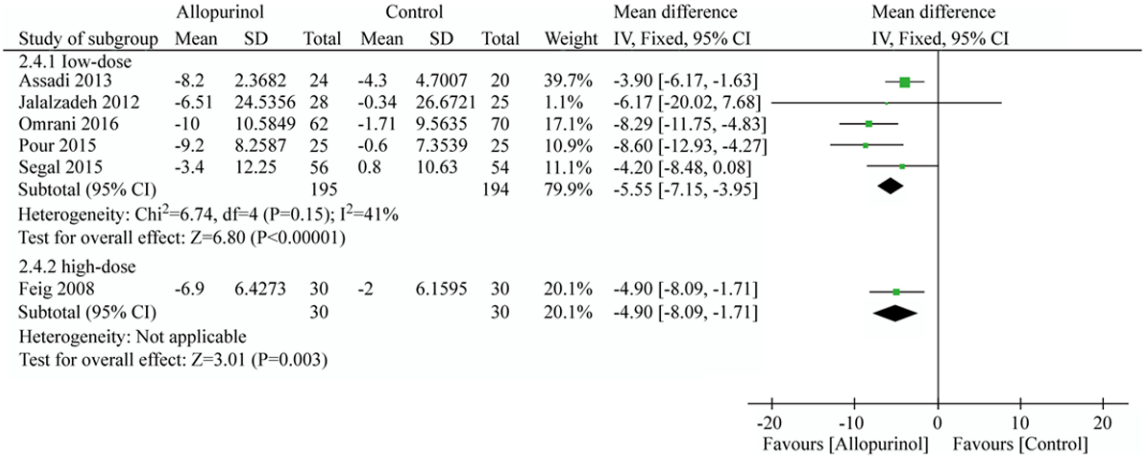


Figure 4. Subgroup analysis of effect of allopurinol on systolic blood pressure according to dose of allopurinol.

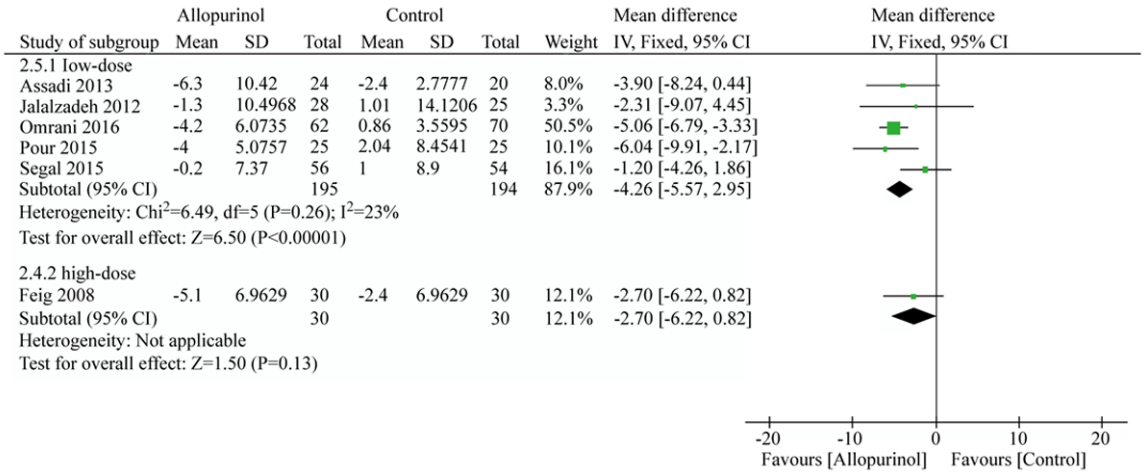


Figure 5. Subgroup analysis of effect of allopurinol on diastolic blood pressure according to dose of allopurinol.

data in changes of serum UA showed high levels of heterogeneity among the results of the studies (heterogeneity X^2, $P < 0.1$, $I^2 = 89\%$), indicating the use of the random-effects model for analysis. Compared with control group, a decline in the level of serum UA was detected in the allopurinol group (MD = 2.05, 95% CI = 1.32-2.78, P < 0.001) (**Figure 3C**).

Subgroup analysis

The analysis based on age stratification revealed that compared with the control group, both of the adults (aged > 18 years) and adolescents (aged < 18 years) with hypertension in the allopurinol group showed a decline in SBP (adults: MD = 7.18, 95% CI = 4.93-9.44 mmHg, P < 0.001; adolescents: MD = 4.24, 95% CI = 2.39-6.08, P < 0.001) (**Figure 3D**) and in DBP (adults: MD = 4.29, 95% CI = 2.92-5.67, P < 0.001; adolescents: MD = 3.18, 95% CI = 0.44-5.91, P < 0.001) (**Figure 3E**).

A subgroup analysis was performed according to dosage of allopurinol. The results demonstrated that treatment with low-dose allopuri-

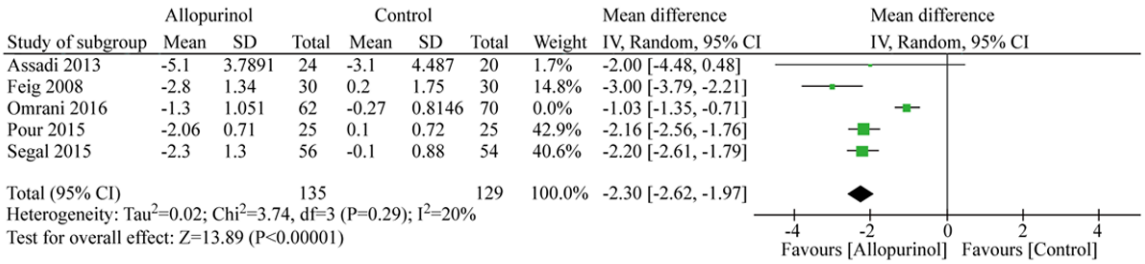


Figure 6. Sensitivity analysis for the effect of allopurinol on serum uric acid.

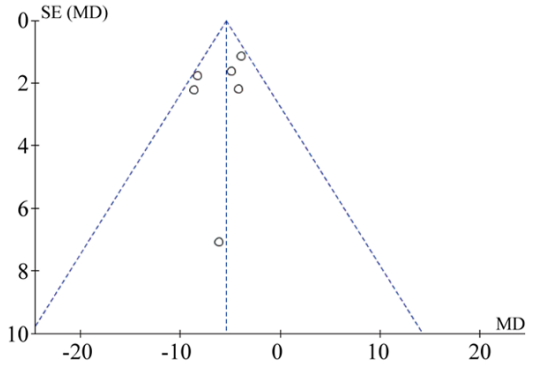


Figure 7. Funnel plots for the effect of allopurinol on systolic blood pressure.

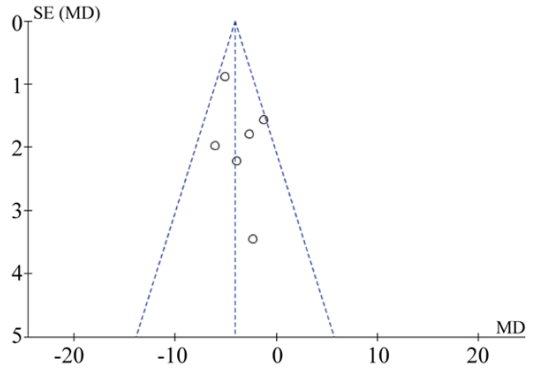


Figure 8. Funnel plots for the effect of allopurinol on diastolic blood pressure.

nol (≤ 300 mg/d) and high-dose allopurinol (> 300 mg/d) both reduced SBP. (low-dose: MD = 5.55, 95% CI = 3.95-7.15 mmHg, P < 0.001; high-dose: MD = 4.90, 95% CI = 1.71-8.09, P = 0.003) (**Figure 4**). There was the effect of low-dose allopurinol on reduction of DBP (MD = 4.26, 95% CI = -2.95-5.57, P < 0.001), but this effect was not seen with high-dose allopurinol treatment (MD = 2.70, 95% CI = -0.82-6.22, P = 0.13) (**Figure 5**). These results, however, need to be interpreted with caution as there was only one study in the subgroup of high-dose allopurinol.

Sensitivity analysis

The data in changes of SUA showed high levels of heterogeneity among the results of the studies. Omrani et al. [27] was the cause of statistical heterogeneity but not clinical heterogeneity according to the sensitivity analysis. Maybe the effects of reduction SUA of allopurinol was covered by hemodialysis (**Figure 6**).

Publication bias

There was no publication bias was found for the effect of allopurinol of BP (**Figures 7**, **8**). On the other hand, a significant asymmetry of the funnel plot for the effect of allopurinol on serum uric acid, which may be due to publication bias and other causes (**Figure 9**).

Adverse event

Only the study by Segal et al. [26] reported the adverse events, such as headache, dizziness, muscle pain, upper respiratory tract or lung infection, with an incidence of 57% in the treatment group and 96% in the control group. No data associated with the incidence of adverse reactions were recorded in the other six studies [13, 23-25, 27].

Discussion

The included six studies aimed to evaluate the influence of allopurinol on the BP of patients with hypertension as well as its safety. The results of the present study showed a significant decrease in SBP, DBP and serum UA in the patients with hypertension in allopurinol group compared with control group. According to MacIsaac et al. [28], anti-hypertension effect of allopurinol was only observed in

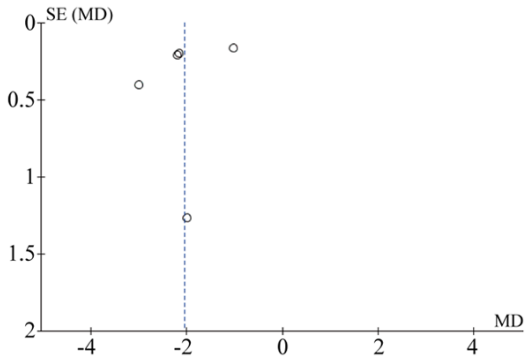


Figure 9. Funnel plots for the effect of allopurinol on serum uric acid.

teenagers, but not certain in the elderly. Accordingly, a subgroup analysis was performed on the basis of age, with a finding that allopurinol presented the antihypertensive effect on both of adults (> 18 years) and adolescents (< 18 years) patients with hypertension.

The degradation of purine nucleotide results in uric acid, which is the last step of xanthine oxidoreductase medicated process. Under normal conditions, the activity of xanthine oxidoreductase generates oxidative substances. Such oxidative substances are also subject to the regulation and degradation of some enzymes. The increase of activity of xanthine oxidoreductase will cause insufficient regulation and degradation of oxidative substances by enzyme activity. This will lead to accumulation of oxidative substances, resulting in decrease of NO generation and thus endothelium dysfunction. Mazzali et al. [29] revealed in a study that hypertension occurred in drug induced hyperuricemia rats, and with the decrease of serum uric acid, the blood pressure can return to normal. Possible mechanism: (1) The uric acid can activate rennin-Angiotensin system and down regulate NO generation, thus cause arteriolar vasoconstriction; (2) The uric acid can cause smooth muscle cell proliferation and afferent glomerular arteriosclerosis [30]. Khosla et al. [31] revealed in a study that increased uric acid can stimulate C-reactive protein production and inhibit endothelial cell proliferation and cause vascular endothelial dysfunction by affecting vascular endothelial cells and smooth muscle cells. Vascular endothelial dysfunction plays an important role in both the onset [32] and progress [33] of hypertension. The uric acid is one of the main free-radical scavengers and metal ion chelating agents in the blood. At preset, it is generally believed that the uric acid plays both pro-oxidant stress and anti- oxidant stress effects [34, 35]. Both in vitro and in vivo studies revealed that intracellular uric acid can cause strong pro-oxidant stress, and the use of blocker and other methods can prevent it from entering the cell and thus effectively relieve the occurrence of oxidant stress.

Previous population-based clinical studies indicated hyperuricemia as one of the pathogeneses leading to hypertension but with little understanding on its mechanism [4, 10, 36, 37] except for the presumptions that hyperuricemia may precipitate hypertension via inflammatory injuries, endothelial dysfunction as well as disorder of renin-angiotensin-aldosterone system [30-33, 38], and that the UA level is closely associated with some other risk factors of cardiovascular diseases such as declined kidney function, increased oxidative products, obesity and metabolic syndrome [34, 39-43]. As a result, the uncertainty has been existing on the correlation between UA level and hypertension. Moreover, inconsistent conclusions have been drawn from different studies concerning the anti-hypertensive effect of allopurinol, a xanthine oxidase inhibitor which has been widely used in clinical practice to lower the serum UA for gout patients.

Three systematic reviews have examined the effect of allopurinol on BP, including a Cochrane Database Systematic Review in 2013 [44] which showed that treatment with allopurinol was associated with a significant reduction of BP. But only one RCT was included in this review, with a small sample size of 30 adolescent hypertension patients involved. In contrast, this study included six RCTs with an involvement of 419 cases including adult patients with Hypertension, and a 2013 systematic review and meta-analysis by Agarwal et al. [18] included 9 RCTs and 1 cohort study with 738 participants, the overall results showed that treatment with allopurinol was associated with small but significant decrease of BP (SBP decrease: 3.3 mmHg, 95% CI = 1.4 to 5.3 mmHg, P = 0.001; DBP decrease: 1.3 mmHg, 95% CI = 0.1 to 2.5 mmHg, P = 0.03). Different from cohort studies whose representati-

veness is always compromised by factors such as research bias and confounding effects, the present study established its inclusion criteria in strict accordance with the requirements of the randomized controlled trials, and thus had a higher credibility. The study by Qu et al. [45] included 15 RCTs and 1111 patients, with a result showing that patients treated with allopurinol had a greater reduction in BP than those in the control group. Compared with the studies by Agarwal et al. [18] and Qu et al. [45] where population with normal BP were also included, this study is more closely associated with clinical practice and thus can be used as a better guidance for treatment as only patients with a confirmed diagnosis of hypertension were included. Qu et al. [45] results demonstrated that treatment with low-dose allopurinol (≤ 300 mg/day) reduced SBP (0.329, 95% CI = 0.116 to 0.542, P = 0.002) as compared to no allopurinol treatment, but this effect was not seen with high-dose allopurinol (> 300 mg/day) treatment (0.030, 95% CI = -0.476 to 0.536, P = 0.908)). There was no difference of the effect of high- or low-dose allopurinol on reduction of DBP (low dose: 0.176, 95% CI = -0.004 to 0.356, P = 0.055; high dose: 0.087, 95% CI = -0.419 to 0.594, P = 0.735). A subgroup analysis was performed according to dosage of allopurinol, this study shows High-(≤ 300 mg/d) or low-(> 300 mg/d) dose allopurinol were associated with a significant reduction in SBP as compared to control group. Similarly, significant reduction of DBP was found in low-dose allopurinol. The reason for this result was its population was hypertension, not similarly with Qu et al. [45] which included normal or pre-hypertension population. So, the effect of allopurinol for hypertension with hyperuricemic may was more effective at reducing BP than non-hypertension.

Although adverse events were reported in only one study [26], there was study showing that about 0.38% of the hospitalized patients presented adverse reactions after allopurinol administration [46], including acute renal failure, hepatitis, toxic epidermal necrolysis, fever, leukocytosis and allergy syndrome. As allopurinol is eliminated mainly through the kidney, a higher rate of adverse reactions are usually observed in patients with renal insufficiency.

Limitation of this study is considered to be the high selective bias due to the detailed randomization described and allocation concealment used in only one study. Little influence is imposed on the results of this study with or without the use of blind method as the primary endpoint is an objective indicator, but the adverse reactions assessed as a secondary endpoint is a subjective indicator, leading to the performance bias in the evaluation procedure. Since dose-effect relation between allopurinol and the endothelial function was identified by some study [15], the dose difference in allopurinol groups from different studies may compromise the evaluation on its anti-hypertensive effect and safety [13, 23-25] OUT of the five studies were based on small sample with the absence of reports on the adverse events, resulting in a lowered accuracy in safety evaluation. Therefore, strict random assignment and allocation concealment shall be used in the following studies to ensure a better inter-group comparability and a lowered bias, and the follow-ups shall be improved to allow a more accurate evaluation on the endpoints.

In conclusion, allopurinol produced significant changes in systolic and diastolic BP. Allopurinol may be utilized as adjunctive antihypertensive agents in select hypertension with underlying hyperuricemia while closely monitoring for any adverse effect.

Disclosure of conflict of interest

None.

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