Efficacy and Safety of Different Doses of Urico-Lowering Agents in The Treatment of Gout with Hyperuricemia: A Systematic Review and Network Meta-Analysis

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Abstract. Objectives**:** To systematically evaluate the efficacy and safety of different doses of uric acid-lowering drugs (allopurinol, febuxostat, and benzbromarone) in patients with gout with hyperuricemia by using the method of reticulated Meta-analysis. Methods: Published clinical randomized controlled trials (RCTs) on the efficacy and safety of febuxostat, allopurinol, and benzbromarone in the treatment of gout with hyperuricemia were searched. Results**:** A total of 17 papers randomized controlled publications met the criteria were included, including 3461 patients (The actual number of people completed 2797) patients actually completed. Mesh meta-analysis showed that 120 mg of febuxostat had better clinical efficacy than other drugs (cumulative probability ranking curve (SUCRA) was 98.5%); 120 mg of febuxostat showed better efficacy in terms of safety than other drugs (cumulative probability ranking curve (SUCRA) was 72.0%). Conclusion: The efficacy and safety of 120 mg febuxostat in the treatment of gout with hyperuricemia were superior to other uric acid lowering drugs. This review recommended 120 mg of febuxostat for the treatment of patients with gout with hyperuricemia.

1 Introduction

Gout is a crystal-associated arthropathy due to monosodium urate (MSU) deposition, which is directly related to hyperuricemia caused by disturbances in purine metabolism (or) reduced uric acid excretion[1]. According to the study of Mats Dehlin et al, the prevalence and incidence of gout were increasing year by year globally, in which serum uric acid (SUA) level was one of the most important risk factors for gout. Therefore, gout with hyperuricemia has become a serious threat to human health, and the search for effective treatments was imminent.

At present, for the treatment of gout with hyperuricemia, uric acid-lowering drugs play an important role in addition to lifestyle changes. The mechanism of urico-lowering drug therapy mainly includs two methods. One is to reduce serum xanthine oxidation inhibitors by inhibiting the synthesis of uric acid[2] such as allopurinol, febuxostat, etc. The metabolic product of allopurinol, allopurinediol, competitively occupies the molybdopterine group, thereby reducing the activity of xanthine oxidase (XO) and the generation of uric acid. However, allopurinol molecules themselves contain purine groups, which can affect other metabolic pathways of purines and are considered one of the mechanisms of allopurinol related adverse reactions[3] .

Another is to increase the excretion of uric acid in the body. For example Benzbromarone reduces uric acid reabsorption and promotes uric acid excretion by inhibiting the uric acid transporter protein (URAT1) on the surface of renal tubular epithelial cells. However, benzbromarone had potential liver toxicity and a risk of inducing hepatitis, and should be used with caution in patients with existing liver disease[4] .

In this paper, three commonly used uric acid-lowering drugs (allopurinol, febuxostat, and benzbromarone) were selected to conduct a reticulated meta-analysis on the efficacy and safety of patients with gout with hyperuricemia dose range. The efficacy of allopurinol, febuxostat and benzbromarone in the treatment of gout combined with hyperuricemia were studied to provide theoretical basis for clinical treatment.

2 Methods

2.1 Inclusion criteria

At first, the study type was a randomized controlled trials. Secondly, Select research subjects based on gout American Rheumatology Association standardand diagnostic criteria in the Chinese consensus on hyperuricemia. Thirdly, the intervention included allopurinol, febuxostat, benzbromarone, and placebo.

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2.2 Exclusion Criteria

At first, valid outcome data cannot be extracted from the text; Secondly, duplicate literature; Thirdly, the clinical diagnosis of the subjects was not clear, or the clinical accompanied by secondary hyperuricemia; medical treatment is non-pharmacological; accompanied by clinically significant and other diseases.

2.3 Search strategy

Based on the PICOS framework, computer searches were conducted in the databases of Cochrane Library, PubMed, Embase, CNKI, Web of Science, Wanfang, Wip, and CBM from inception to December 2022.

2.4 Literature screening and data extraction

Screening process, data extraction, and bias risk based on the research method of Shengzhao Zhang et al[5].

2.5 Statistical methods

Use Stata 17.0 software for data analysis, processing, and plotting.

3 Results

3.1 Literature search results and basic characteristics of included studies

A total of 1701 literatures were obtained by searching the database, and 608 literatures were obtained after preliminary screening. By reading the titles and abstracts, 439 literatures were excluded from non-randomized controlled trials, duplicate publications, and literatures that did not match the content of this study. The remaining 169 literatures required in-depth reading of the full text to exclude those that did not conform to the evaluation of this systematic review. A total of 17[1-4, 6-18] literatures were ultimately included in the final inclusion criteria, including 3306 patients. In this paper, 15[1, 3, 6-18] papers included mentioned the method of random allocation of specific assignments. 2 papers[2, 6] included mention allocation hiding. 3 papers[2, 7, 8] mentioned that subjects were blinded. The inclusion of 17 papers of literature all mentioned that the baseline period of the control group and the experimental group were comparable.

3.2 Results of Net Meta-Analysis of Clinical Efficacy

3.2.1 Web evidence for comparison of clinical efficacy

Of the 17 papers included in this study with efficacy as the study outcome indicator, provided blood uric acid values for seven interventions. (Fig. 1A), the thickness of the lines was related to the frequency of the study, and the size of the dots was related to the size of the study sample size, and interconnected dots represented the existence of a direct comparison between two interventions, and unconnected dots represented the existence of an indirect comparison between two interventions. The seven interventions formed a total of seven triangular closed loops. Tested Prob>chi2=0.069 7 (>0.05).

3.2.2 Comparison of clinical efficacy of treatment measures

Stata17.0 was used to plot cumulative ranked probability plots (Fig. 1B), and the surface area under the cumulative curve was used as an evaluation index to rank the comparative efficacy results of each treatment measure from high to low. C (98.5%) > D (80.3%) > E (58.6%) > F (54.1%) > A (41.1%) > H (40.6%) > B (26.5%) > G (0.4%). 120 mg febuxostat was the best intervention in terms of clinical efficacy.

3.2.3 Net Meta-analysis of Clinical Efficacy of Therapeutic Interventions

Stata17.0 was used to draw the network forest map (Fig. 1C) and the ranking table (Fig. 2) for two-by-two comparison. The results showed that C (120 mg febuxostat), D (80 mg febuxostat), E (40 mg febuxostat), F (20 mg febuxostat), A (300 mg allopurinol), H (100 mg phenylbromarone), and B (200 mg allopurinol) had better clinical efficacy than G (placebo) during the treatment period than G (placebo). 120 mg febuxostat was more effective than B (200 mg allopurinol), E (40 mg febuxostat), and D (80 mg febuxostat) in treating patients with gout with hyperuricemia; C (120 mg febuxostat) and D (80 mg febuxostat) were more effective than A (300 mg allopurinol) were more effective in treating patients with gout with hyperuricemia, and the rest were not significant.

3.2.4 Publication bias in treatment assessment

Stata17.0 was used to draw the correction-funnel plot (Fig. 1D), the funnel plot was roughly symmetrical, but there were differences between the left and right sides, which revealed a possible publication bias or small sample effect in this study.

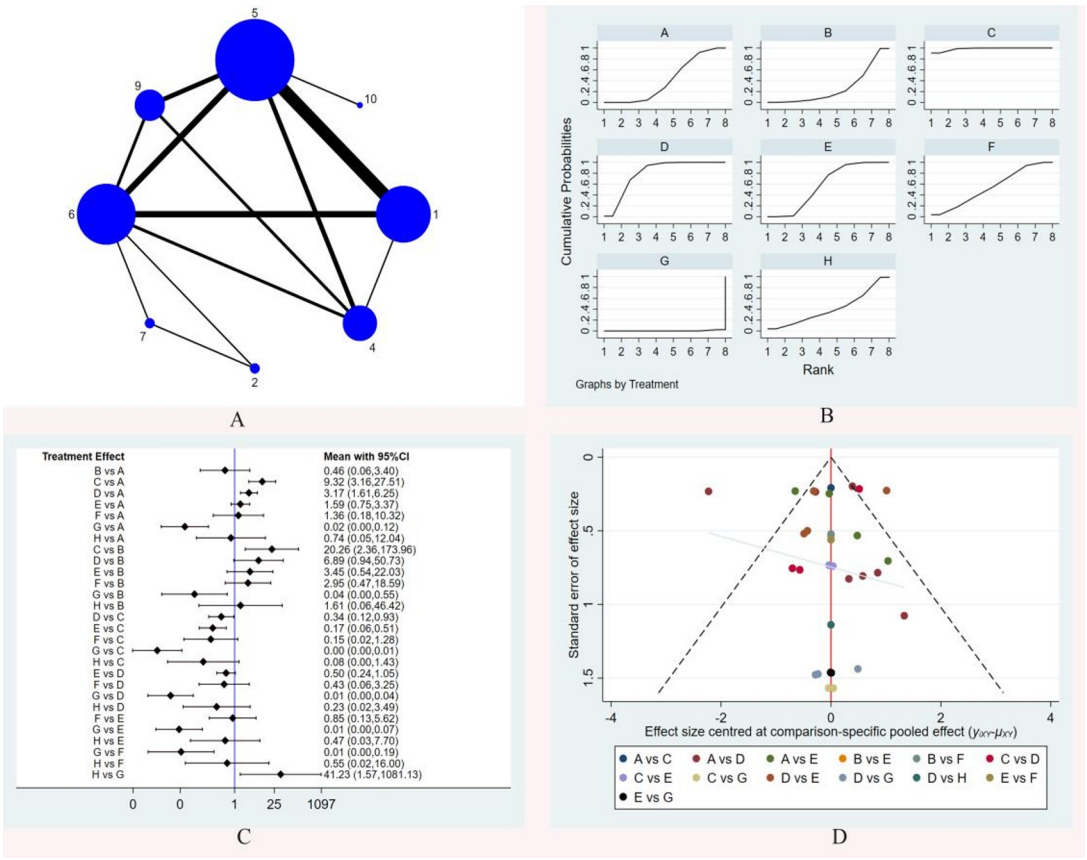

Fig. 1. Evidence network of efficacy. (A) Cumulative probability rank of efficacy.(B) Intervalplot of efficacy.(C) Funnel plot for correction comparison of efficacy.(D). (*A.300 mg allopurinol; B.200 mg allopurinol; C.120 mg febuxostat; D.80 mg febuxostat; E.40 mg febuxostat; F.20 mg febuxostat; G. placebo H.100 mg Benzbromarone*).

C							
2.94 (1.07,8.08)	D						
5.87 (1.97,17.47)	1.99 (0.95,4.20)	E					
6.86 (0.78,60.52)	2.33 (0.31,17.68)	1.17 (0.18,7.70)	F				
9.32 (3.16,27.51)	3.17 (1.61,6.25)	1.59 (0.75,3.37)	1.36 (0.18,10.32)	A			
12.58 (0.70,225.80)	4.28 (0.29,63.96)	2.15 (0.13,35.45)	1.83 (0.06,53.78)	1.35 (0.08,21.95)	H		
20.26 (2.36,173.96)	6.89 (0.94,50.73)	3.45 (0.54,22.03)	2.95 (0.47,18.59)	2.17 (0.29,16.05)	1.61 (0.06,46.42)	B	
518.84 (70.94,3794.43)	176.44 (28.25,1101.99)	88.45 (13.46,581.11)	75.60 (5.27,1084.13)	55.68 (8.27,375.03)	41.23 (1.57,1081.13)	25.61 (1.83,359.49)	G

Fig. 2. Network Meta-analysis of the efficacy of each measure.

3.3 Results of reticulated Meta-analysis of adverse reactions

3.3.1 Web evidence for comparison of adverse reactions

Of the 19 papers included in this study that used adverse reactions as the study outcome indicator, only 14 papers provided patients with adverse reactions involving 10 interventions (Fig. 3A). The 10 interventions formed a total of eight triangular closed loops. The reticulated evidence map showed the presence of 8 closed loops, so inconsistency tests were required. In the loop test, the lower limit of the 95% CI in 6 closed loops did not reach 0, which suggested that these 6 loop inconsistencies were not statistically significant (Fig. 3B).

3.3.2 Results of the comparison of adverse reactions

Stata 17.0 was used to draw a cumulative ranking probability plot (Fig. 3C), and under surface area of the cumulative curve was used as an evaluation index, the results of the comparison of adverse reactions for each treatment measure were ranked in descending order. (72.0%) > H (67.9%) > G (66.5%) > E (62.2%) > F

(60.8%) > B (55.3%) > I (44.0%) > A (29.5%) > J (22.7%) > C (11.0%). The results showed that 120 mg febuxostat was the best intervention in reducing adverse effects in patients.

3.3.3 Net Meta-analysis for Comparison of Adverse Reactions

A two-by-two comparison of reticulated forest plot (Fig. 3D) and league table (Fig. 4) using stata 17.0. The results showed that 120 mg febuxostat, placebo, 80 mg febuxostat, and 40 mg febuxostat were effective in reducing patients' adverse reactions over 100 mg of allopurinol during the treatment period. 120 mg febuxostat combined with 80 mg febuxostat were effective in reducing patients' adverse reactions over 300 mg of Allopurinol was effective in reducing patient adverse reactions, and the rest were not significant.

3.3.4 Assessment of publication bias

Correction-funnel plots were drawn using stata17.0, and (Fig. 3E), the funnel plots were more asymmetric, which revealing that there may have been a publication bias or a small sample effect in this study.

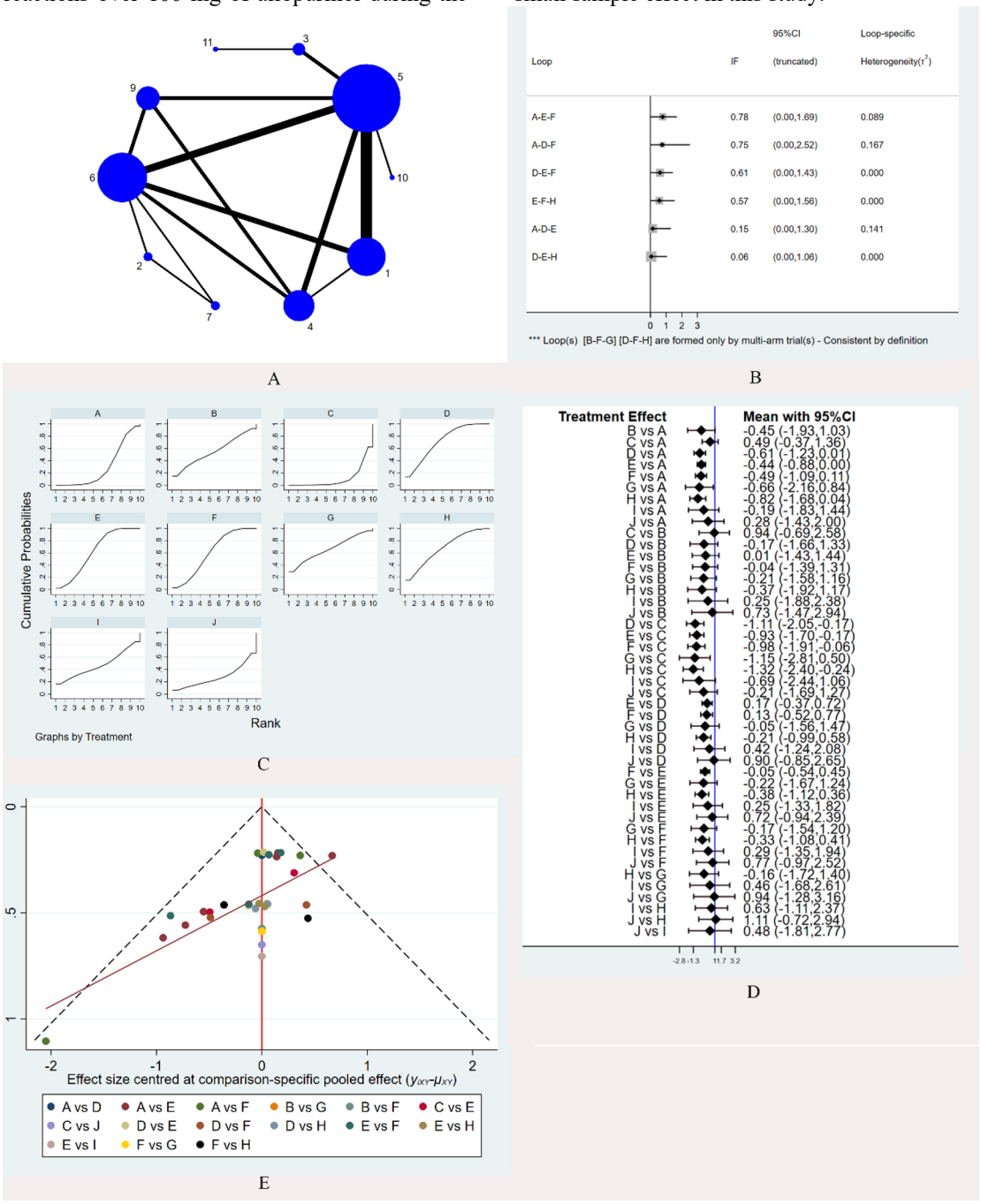

Fig. 3. Evidence network of adverse reactions. (A) Inconsistency test results of closed loop of adverse reaction of various measures. (B) Cumulative probability rank of adverse reactions. (C) Intervalplot of difference of adverse reactions. (D) Funnel plot for correction comparison of adverse reactions (F). (A:300 mg allopurinol; B:200mg allopurinol; C:100mg allopurinol; D:120 mg febuxostat; E:80 mg febuxostat F:40 mg febuxostat; G:20 mg febuxostat; H:placebo; I:100 mg benzbromarone; J: 50 mg benzbromarone).

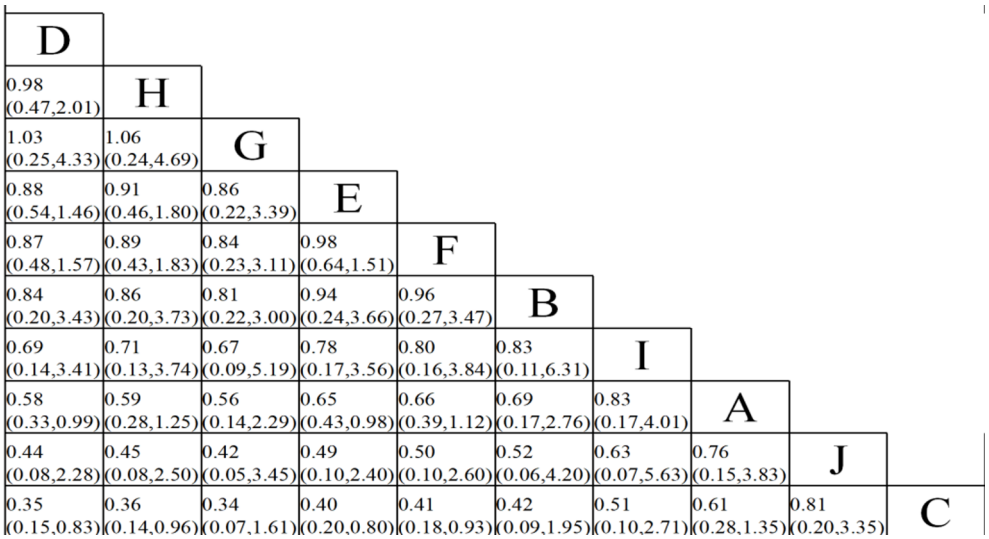

Fig. 4. Network Meta-analysis of adverse reactionsnotes.

4 Discussion

This study systematically evaluated the efficacy and safety of different doses of uric acid-lowering drugs in the treatment of gout with hyperuricemia. The results confirmed that all three uric acid-lowering drugs at different doses were effective in treating gout with hyperuricemia compared with placebo. The results showed that the clinical therapeutic efficacy of 120 mg febuxostat was significantly better than other two uric acid-lowering drugs. Febuxostat is a xanthine oxidase inhibitor, which is mainly metabolized in the liver and excreted by the urinary system and the intestinal tract[2] and it is mainly used to reduce serum uric acid levels in patients with allopurinol intolerance or non-response[5]. Compared with allopurinol, febuxostat can effectively inhibit the reduction and oxidation of xanthine oxidase without affecting other functional enzymes involved in purine metabolism, thus achieving effective inhibition of uric acid synthesis[4, 6]. Febuxostat not only has a significant efficacy in lowering serum urate, but also can significantly improve the frequency of gouty attacks[9].

The results showed that 120 mg of febuxostat was the best intervention while causing fewer adverse effects, 100 mg of allopurinol caused the most adverse effects in patients and also caused rashes, gastrointestinal and other reactions in patients and similar results were obtained in a study by Sun Shanshan[19]. However, compared with allopurinol, it has limited studies and insufficient data compared to allopurinol and may have the risk of causing cardiovascular disease, and studies have shown that in adverse events related to cardiac disease caused by febuxostat and allopurinol, users of febuxostat have a higher risk of cardiovascular disease compared to users of allopurinol.

5 Conclusion

There are still some limitations in this study. Firstly, the number of patients included in the literature was not unevenly distributed. Most trials recruited less than 100 patients in each dose group, Xinfang HUANG, and others recruited more than 170 patients in each dose group, and even Michael A. Becker recruited more than 250 patients in each dose group, which may cause the analysis to be limited and lead to problems such as heterogeneity in the results of the analysis. Therefore, more findings are needed to verify this conclusion and provide more valuable evidence-based rationale for the treatment of gout with hyperuricemia.

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