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Original Article

# Efficacy of Allopurinol and Febuxostat in the Treatment of Gout with Hyperuricemia – A Comparative Study

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## ABSTRACT

***Objective***: To compare the efficacy and effectiveness of Allopurinol with Febuxostat in the treatment of gout in hyperuricemia patients.
***Study Design***: Quasi Experimental study.
***Place and Duration of Study***: Department of Medicine, Pak-Emirates Military Hospital, Rawalpindi Pakistan, from Jan to Dec 2024.
***Methodology***: Patients aged 18-75 years, diagnosed with gout having serum uric acid levels >6.8 mg/dL were included. Patients were divided in two groups of 35 patients each. Group-A was given Allopurinol and Group-B was given Febuxostat. Serum uric acid levels measured at baseline and then at 2 weeks, 4 weeks and 6 weeks follow-ups and compared. Change of uric acid levels at each follow-up and mean reduction was compared between the two groups.
***Results***: Seventy patients were enrolled with median age of 45.00(18.00) and 45.00(11.00) in Group-A and Group-B respectively. At baseline, mean serum uric acid levels were 8.06±0.61 mg/dL in the Group-A and 8.24±0.74 mg/dL in the Group-B ($p$=0.410). In the Group-A, serum uric acid significantly decreased from baseline 8.08±0.61 to 5.78±0.50 mg/dL at 6 weeks ($p$<0.05), and in Group-B declined from baseline 8.24±0.74 to 5.16±0.74 mg/dL at 6 weeks follow-up ($p$<0.05). The mean reduction in serum uric acid from baseline to 6 weeks (delta uric acid) was 2.27±0.38 mg/dL in the Group-A and 3.11±0.50 mg/dL in group-B.
***Conclusion***: While both drugs effectively lowered serum uric acid, Febuxostat was significantly more effective in achieving target levels within 6 weeks.

**Keywords**: Allopurinol, Febuxostat, Gout, Hyperuricemia, Uric Acid.

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## INTRODUCTION

Hyperuricemia, a considerable risk factor for gout and arthritis, ischemic heart disease (IHD), cardiovascular accident, diabetes, metabolic syndrome and renal failure.[1] Uric acid, a breakdown product of purine metabolism, renal excretion with urate solubility limit of ≤6.8mg/dL.[2] Excessive exogenous intake of meat, fructose, flavonoids, and alcohol contributes to increased serum uric acid levels which increases the risk of developing gouty arthritis and has been linked with cardiovascular and renal adverse events.[3] As per US National Health and Nutrition Examination Survey (NHANES), overall prevalence of hyperuricemia is 20.2% in men and 20.0% in women.[4]

Gout, one of the clinical manifestation of hyperuricemia, affects men more than women with global prevalence of 1.2-4.1%[5] with prevalence of 5.9% in men and 2.7% in women in Pakistan.[6] Serum Uric acid more than 6.8 mg/dL can lead to urate crystals formation causing renal stones, and tophi in joints causing gouty arthritis.[7] Growing evidence suggests that inter-individual and inter-population variability in drug response may be influenced by genetic factors, including single nucleotide polymorphisms (SNPs) affecting drug-metabolizing enzymes and transporters. For example, polymorphisms in genes such as ABCG2, HLA-B58:01, and XDH (xanthine dehydrogenase) have been shown to influence both the efficacy and safety of urate-lowering therapies.8 These pharmacogenomics variations may lead to differential responses to Allopurinol and Febuxostat among diverse ethnic groups, underscoring the importance of region-specific comparative studies.

A paucity of local data available regarding comparative efficacy of two common urate lowering agents, Allopurinol and Febuxostat to achieve target serum uric acid of <6.0mg/dL. Moreover, Febuxostat costs around 9 times more as compared to Allopurinol, so a comparison is warranted for cost-benefit ratio in a developing country. The rationale for

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conducting this was to compare the efficacy of Allopurinol and Febuxostat to achieve target serum uric acid levels in patients of gout with hyperuricemia.

## METHODOLOGY

This Quasi experimental study was conducted at the outpatient medical clinics of Pak Emirates Military Hospital, Rawalpindi, Pakistan from Jan to Dec 2024. The study was conducted following approval from hospital ethical review committee (ERC:A/28/ERC/593/23Oct2023). The sample size was calculated using OpenEpi online sample size calculator taking confidence level 95%, margin of error 5% and mean change in serum uric acid levels of -44.73±19.10 with Febuxostat 80 mg and -32.99±15.33 with Allopurinol 300 mg as reported by Becker *et al*.[9] The estimated sample size came out to be 70 (35 patients each group). Non-probability consecutive sampling technique was employed, enrolling all eligible patients who met the criteria during the study period.

**Inclusion Criteria**: Adult patients of either gender, aged 18-75 years, diagnosed with gout with documented serum uric acid levels of >6.8 mg/dL, and were due to be started on either Allopurinol or Febuxostat after resolution of acute gout attack were included.

**Exclusion Criteria**: Patients having any history of hypersensitivity or contraindications to Allopurinol or Febuxostat, having severe renal impairment (eGFR <30 mL/min/1.73 m²), known chronic liver disease or active malignancy, pregnant or lactating women or already on urate-lowering therapy were excluded.

All patients attending the medical outpatient department and diagnosed with acute gouty arthritis based on clinical history, examination, and confirmed hyperuricemia (serum uric acid >6.8 mg/dL) were evaluated for eligibility. Total 112 patients with hyperuricemia screened and scrutinized for inclusion in study and 90 patients 45 in each group were included in the study. Total 70 patients with 35 in each group were included in final analysis after completion of predefined follow-ups (Figure).

During the initial presentation, all patients received appropriate management for acute gout, including Nonsteroidal Anti-inflammatory drugs (NSAIDs), Colchicine, or Corticosteroids as clinically indicated. Urate-lowering therapy was not initiated during the acute phase; instead, it was started a few days after resolution of the acute attack, in line with standard clinical guidelines. Patients were then started on either Allopurinol 100 mg or Febuxostat 40 mg based on physician discretion and clinical suitability. Allopurinol was increased to 200 mg or 300 mg as needed after every 2 weeks, whereas the dose Febuxostat was kept the same during the study duration. As the study was observational, no randomization or blinding performed. Baseline characteristics such as age, gender, body mass index (BMI), comorbidities, and baseline serum uric acid levels were documented. Serum uric acid levels measured at baseline before initiating urate-lowering therapy and then monitored at three follow-up points: 2 weeks, 4 weeks and 6 weeks after initiation of therapy. Therapeutic efficacy assessed by comparing serum uric acid levels at each follow-up with baseline. Any adverse effects or discontinuation of therapy were also recorded.

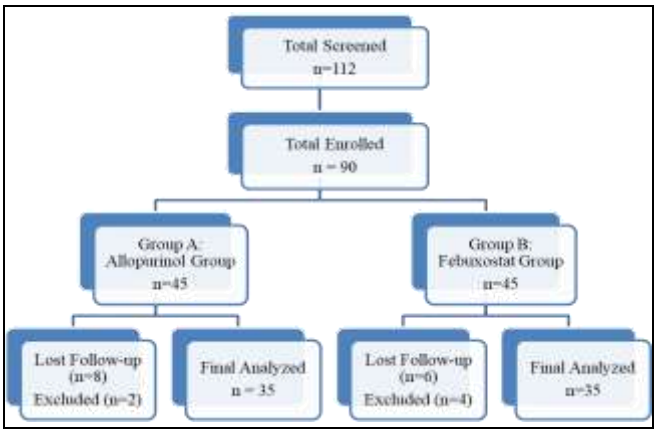


**Figure: Summary of Enrollment and Analysis Process**

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 25. The normality of continuous data was assessed using the Shapiro–Wilk test. Continuous variables including age, uric acid levels at baseline and follow-up, change in uric acid levels, and BMI were presented as Mean±SD or median [IQR] whereas categorical variables such as gender, comorbid and adverse effects were represented as frequency and percentages. Mean reduction in serum uric acid was compared between the two groups using an independent samples t-test. Mann Whitney U test used for ag and BMI. Chi-square test was used for qualitative variables. A *p*-value of ≤0.05 was considered statistically significant.

## RESULTS

Seventy patients were enrolled including 35 patients in each group with median age of 45.00(18.00)

and 45.00(11.00) in Group-A and Group-B individuals respectively ($p$=0.324). Baseline characteristics, including age, gender distribution, body mass index (BMI), comorbidities, and initial serum uric acid levels, were comparable between both groups. Statistical analysis showed no significant differences in these variables between the two treatment groups ($p$>0.05 for all comparisons) (Table-I).

**Table-I: Comparison of Baseline Characteristics of Study Participants(n=70)**

| Variable(s) | | Group-A (Allopurinol) (n=35) | Group-B (Febuxostat) (n=35) | *p*-value |
|---|---|---|---|---|
| Age (years), median [IQR] | | 45.00(18.00) | 45.00(11.00) | 0.324 |
| Gender, n(%) | Male | 21(60.0%) | 18(51.4%) | 0.470 |
| | Female | 14(40.0%) | 17(48.6%) | |
| BMI (kg/m²), median [IQR] | | 27.40(4.40) | 26.42(3.80) | 0.274 |
| **Comorbidities** | | | | |
| Diabetes, n(%) | | 6(17.1%) | 5(14.3%) | 1.00 |
| Hypertension, n(%) | | 10(28.6%) | 4(11.4%) | 0.067 |
| Ischemic Heart Disease, n(%) | | 4(11.4%) | 2(5.7%) | 0.673 |
| Hypothyroidism, n(%) | | 4(11.4%) | 5(14.3%) | 1.00 |
| Obesity, n(%) | | 8(22.9%) | 5(14.3%) | 0.540 |
| Chronic kidney disease, n(%) | | 6(17.1%) | 2(5.7%) | 0.259 |
| Baseline Serum Uric Acid (mg/dL), Mean±SD | | 8.06±0.61 | 8.24±0.74 | 0.410 |

Comparison of serum uric acid levels at each follow-up visit demonstrated significant differences between both studied groups. At baseline, mean serum uric acid levels were 8.06±0.61 mg/dL in the Group-A and 8.24±0.74 mg/dL in the Group-B ($p$=0.410). At 2 weeks, the levels were 7.60±0.57 vs. 7.39±0.76 mg/dL ($p$=0.095). However, at 4-weeks and 6-weeks follow up serum uric acid levels were 6.84±0.55 vs. 6.25±0.85 mg/dL at 4-weeks ($p$=0.001), and 5.79±0.50 vs. 5.14±0.74 mg/dL at 6-weeks in Group-A and Group-B respectively ($p$<0.001) (Table-II).

**Table-II: Comparison of Serum Uric Acid Levels Among Groups (n=70)**

| Serum Uric Acid Levels (mg/dL) | Group-A (n=35) | Group-B (n=35) | *p*-value |
|---|---|---|---|
| Baseline, Mean±SD | 8.06±0.61 | 8.24±0.74 | 0.410 |
| 2 Weeks, Mean±SD | 7.60±0.57 | 7.39±0.76 | 0.095 |
| 4 Weeks, Mean±SD | 6.84±0.55 | 6.25±0.85 | 0.001 |
| 6 Weeks, Mean±SD | 5.79±0.50 | 5.14±0.74 | <0.001 |

Within-group analyses revealed a significant reduction in serum uric acid levels over time in both treatment groups. In the Group-A, serum uric acid significantly decreased from baseline 8.08±0.61 to 5.78±0.50 mg/dL at 6 weeks follow-up ($p$<0.05), with post-hoc analysis indicating significant changes from 2 weeks onward. Similarly, the Group-B demonstrated a significant decline from baseline 8.24 ± 0.74 to 5.16 ± 0.74 mg/dL at 6 weeks follow-up ($p$<0.05), with consistent reductions noted at all follow-up points.

The mean reduction in serum uric acid from baseline to 6 weeks (delta uric acid) was 2.27 ± 0.38 mg/dL in the Group-A and 3.11 ± 0.50 mg/dL in the Febuxostat group. This reduction was significantly greater in the Group-B ($p$<0.001), indicating superior efficacy in lowering serum uric acid levels over 6 weeks. Similarly, the percentage decrease in serum uric acid was also higher in the Group-B (37.43% ± 5.54) compared to the Group-A (28.32% ± 3.89) with a statistically significant difference ($p$<0.001). At the end of the 6-week study period, the proportion of patients achieving the target serum uric acid level (≤6.8mg/dL) was significantly higher in the Group-B (88.57%) compared to the Group-A (68.57%) ($p$=0.041). At 4 weeks, 34.2% of Group-B patients achieved target levels, while none did in the Group-A. No patient in either group had reached target levels at 2 weeks.

Regarding adverse events, 25 patients in Group-A and 20 in Group-B reported side effects. The most frequently encountered adverse effects included acute gout, hypersensitivity reactions, and gastrointestinal complaints. There was no statistically significant difference in the total incidence of adverse effects between the groups ($p$=0.378). Therapy discontinuation due to adverse effects occurred with no significant difference between the two groups. (Table-III).

**Table-III: Adverse Effects Comparison between Allopurinol and Febuxostat (n=70)**

| Adverse Effect / Outcome | Group-A (n=35) | Group-B (n=35) | *p*-value |
|---|---|---|---|
| None, n(%) | 10(28.6%) | 15(42.9%) | 0.378 |
| Nausea / Vomiting, n(%) | 2(5.7%) | 5(14.3%) | |
| Hypersensitivity reaction / Skin rash, n(%) | 6(17.1%) | 3(8.6%) | |
| Dyspepsia / Pain Abdomen, n(%) | 5(14.3%) | 3(8.6%) | |
| Acute Gout, n(%) | 12(34.3%) | 9(25.7%) | |

## DISCUSSION

The findings of this study demonstrate that both Allopurinol and Febuxostat effectively reduced serum uric acid levels over a six-week treatment period in patients with gout and hyperuricemia. However, Febuxostat demonstrated superior efficacy at all follow-up points, with a mean reduction of 3.11±0.50 mg/dL compared to 2.27±0.38 mg/dL in the Group-A. By week 6, serum uric acid dropped from 8.24 ± 0.74 to 5.16 ± 0.74 mg/dL in the Febuxostat group, and from 8.08 ± 0.61 to 5.78 ± 0.50 mg/dL in the Group-A. These

findings were in accordance with the results of study by Wang et al. who also concluded that reduction in serum uric acid levels were more significant in Group-Bas compared to Group-A with better efficacy and lesser adverse reactions ($p$<0.005).[10]

In our study, the mean reduction in serum uric acid levels was significantly greater with Febuxostat (3.11 ± 0.50 vs. 2.27 ± 0.38 mg/dL, $p$<0.001), as was the percentage decrease (37.43% vs. 28.32%). In a meta-analysis of RCTs, Xie *et al.,* concluded that target serum uric acid levels (≤6.0mg/dL) were achieved in higher percentage of hyperuricemic patients using Febuxostat (80mg/d) as compared to those who were using Allopurinol (200-300mg/d) [RR=1.79, 95% CI: 1.55-2.08, $p$<0.001].[11] In another study, Liu *et al.,* found similar findings that Febuxostat (40mg/d) achieved target serum uric acid levels (≤6.0mg/dL) at 4-week follow up with better safety profile and lower side effects when compared with Allopurinol (200-300mg/d) ($p$<0.005).[12]

At 6-week follow up, 88.57% of Febuxostat-treated patients achieved the target uric acid level (<6.8 mg/dL), compared to 68.57% in the Group-A ($p$=0.041). This superior urate-lowering effect was also reflected in the higher percentage reduction from baseline and the larger proportion of patients who achieved the target serum uric acid level of <6.8 mg/dL by the end of the study period. In CONFIRMS trail, Becker et al. concluded that higher proportions of patients given Febuxostat (40mg/d) achieved serum uric acid levels (< 6.0mg/dL) as compared to Group-A at 1-month ($p$=0.031) and 2-month ($p$<0.005) follow up.[13] Xu *et al.,* observed in a RCT that primary outcome of target serum uric acid level (<6.8mg/dL) was achieved at 4-week follow up in 33.5% individuals using Febuxostat (80mg/d), 22.5% in patients given Febuxostat (40mg/d) and 17.0% in those who were given Allopurinol (300mg/d) ($p$<0.005).[14] However, O`Dell *et al.,* observed slightly different results where 81.1% patients using Allopurinol achieved target serum acid levels during 5-week follow up period as compared to 78.4% of Febuxostat group.[15]

In this study, adverse events were reported in both groups (25 in Allopurinol, 20 in Febuxostat), but the difference was not statistically significant and no major adverse cardiac event was observed in any patient of either group ($p$=0.378). Wang *et al.,* observed that Febuxostat had better safety profile with lower adverse effects including GI upset and skin rash as compared to Allopurinol (OR=0.55, 95% CI: 0.42-0.73, p<0.001).[16] Zhang *et al.,* also concluded in RCT that Allopurinol and Febuxostat had similar adverse effects and neither Allopurinol nor Febuxostat increased or decreased adverse cardiovascular event (MACE) risk.[17] In another study, Mackenzie *et al.,* observed similar results with 57.2% participants of Group-B had one or more serious side effects as compared to 59.4% of Group-A with no major cardiovascular event in either group.[18]

Despite the difference in efficacy, cost remains a critical factor, especially in resource-limited settings. Febuxostat, priced at approximately PKR 28 per tablet, is significantly more expensive than Allopurinol, which costs around PKR 4 per tablet. Given that both drugs showed comparable safety profiles, with no significant difference in adverse effects or discontinuation rates, the decision to prescribe Febuxostat must consider not only clinical effectiveness but also affordability and accessibility for patients. In this context, while Febuxostat may be more effective for achieving rapid urate control, Allopurinol remains a more economical option.

## CONCLUSION

The findings of this study showed that while both drugs, Febuxostat and Allopurinol, effectively lowered serum uric acid, Febuxostat was significantly more effective in achieving target levels within 6 weeks, with a comparable safety profile to Allopurinol. However, Allopurinol remains a more economical option with modest but meaningful reductions in serum uric acid levels.

## LIMITATIONS OF STUDY

The authors are well aware of the limitation of the study most important being the single-center study and limited sample size. There is the possibility of non-adherence to medication and a large number of participants who lost to follow-up affecting the final analysis and results. The dietary effect was not studied which could have affected reduction in serum uric acid levels. Further studies including control trials are needed with larger sample sets covering multiple centers for more authentic results and widespread implementation on the general population.

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**Authors' Contribution**

Following authors have made substantial contributions to the manuscript as under:

MS & AF: Data acquisition, data analysis, critical review, approval of the final version to be published.

AA & HW: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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