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Comparative Study to Assess the Safety and Effectiveness of Allopurinol & Febuxostat in Patients Diagnosed with Gout

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Abstract **Original Research Article**

Introduction: Gout is placed under the umbrella term 'arthritis' - a wide variety of joint illness and joint pain. Some types of arthritis cause inflammation in the joints, while others do not. It is the most prevalent form of inflammatory arthritis which arises due to the elevated levels of Serum Uric acid (SUA), leading to the deposition of Mono Sodium Urate (MSU) crystals in and around joints. burden of gout has risen in recent decades with a prevalence rate of <1% to 6.8% and the patients with gout may have significant medical comorbidity load asociated with pain, disability and activity limitation which inturn affects the patients' Health-related quality of life (HRQOL). Several drugs are used to treat acute attacks of gout which includes Colchicine, Non steroidal anti inflammatory drugs (NSAIDs), and Corticosteroids. Long term management of gout focuses on lowering SUA level to normal (<0.36mmol/L). There are two major classes of drugs used to reduce SUA levels, Urate-lowering therapy (ULT), specifically Uricosuric drugs and Xanthine oxidase inhibitors (XOIs). Hence, it is necessary to compare the safety and effectiveness of Allopurinol and Febuxostat used in the management of gout and there is a growing need to research the impact of gout on patients' HRQOL inorder to improve productivity and QOL of patients. ***Objectives:*** The goal of the study was to compare the safety and effectiveness of Allopurinol and Febuxostat in patients diagnosed with Gout. The study also aimed to assess the effect of these on renal profile and the study further assessed the Health-related quality of life of the patients. ***Methodology:*** This was an observational study conducted in the selected Orthopedic clinics in T. Dasarahalli, Bengaluru District for a period of 6 months by enrolling 50 subjects, based on various inclusion and exclusion criteria. The subject's demographic details, laboratory data and responses were collected with the help of a self-designed questionnaire. Standardized questionnaire used in the study was 36-Item Short-Form Health Survey (SF- 36). The collected data were entered in Microsoft Excel and appropriate descriptive and inferential statistical analysis was performed. ***Results:*** On comparison of the effectiveness and safety of both Febuxostat and Allopurinol, Febuxostat was found to lower SUA level much faster than Allopurinol. It was also found to have better pharmacokinetics when compared to Allopurinol. The HRQOL was assessed using SF-36 and the overall average for HRQOL of Febuxostat and Allopurinol was found to be 52.3 and 52.1 respectively. ***Conclusion:*** The study found that Febuxostat was more effective than allopurinol with regard to their ability to lower SUA levels. Both the drugs were also found to be safe on renal profile as they are capable of maintaining acceptable Serum Creatinine levels. From this study, it is evident that gout had significant impact on HRQOL of patients and on comparison of overall scores, it was observed that Febuxostat subjects tends to have better QOL. Early treatment strategies to improve disease control may also lead to improvements in the QOL of patients.

Keywords: Allopurinol, Febuxostat, Gout, Serum Uric Acid, HRQOL.

GOUT

Gout is placed under the umbrella term 'arthritis' - a wide variety of joint illness and joint pain. Some types of arthritis cause inflammation in the joints, while others do not. It is the most prevalent form of inflammatory arthritis which arises due to the elevated levels of SUA, leading to the deposition of Mono Sodium Urate (MSU) crystals in and around joints. Uric acid is a heterocyclic compound whose levels in the body depend

on the balance between purine degradation and Uric acid excretion rates. Persistently elevated SUA levels more than 7mg/dl resulting in the super saturation of body tissues with Urate, ends up in crystallization in tissues. Epidemiological studies have reported that the global burden of gout has risen in recent decades with a PR of <1% to 6.8% and an incidence of 0.58 to 2.89 per 1000 person-years. Community Oriented Program for the Control of Rheumatic Diseases (COPCORD) studies estimated that the prevalence of Gout in Indian population was found to have increased from 0.12 to 1.14%.

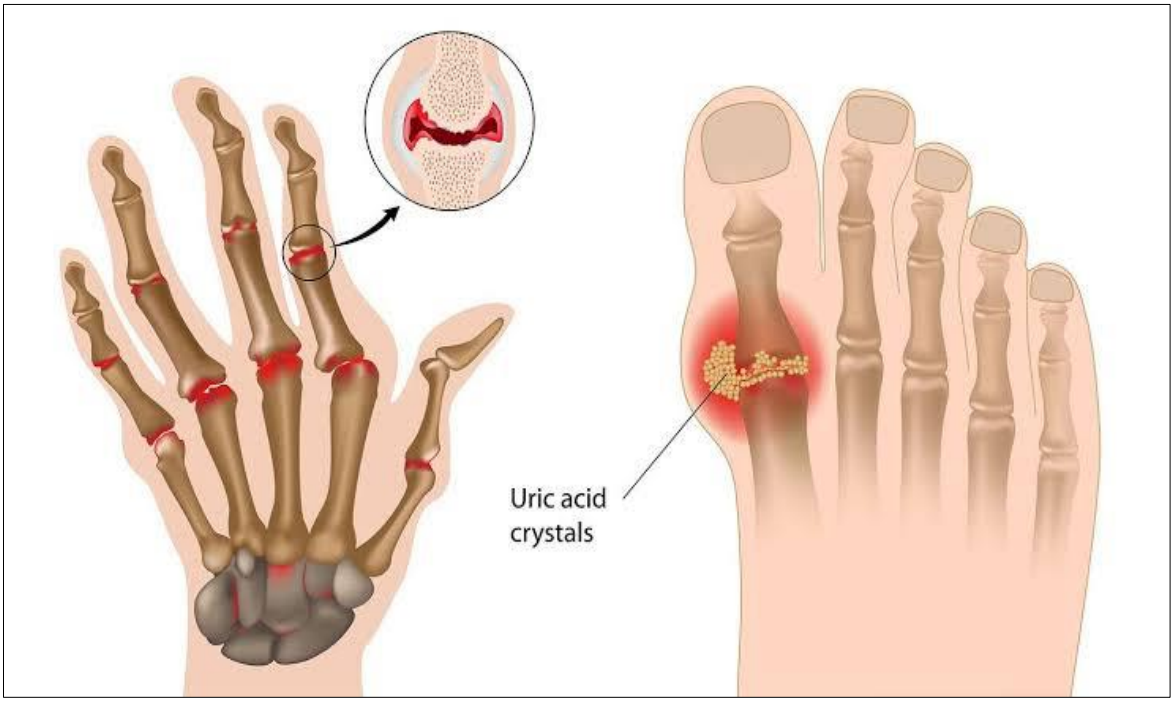

Figure 1: Deposition of Monosodium urate crystals in gout patients.

Table 1: Prevalence of gout in different countries around the world.

Country	Data collection period	Prevalence (%)
Australia	2015	6.8
Canada	2000-2012	3.8
China	2000-2016	1.1
Nigeria	2015-2016	0.1
UAE	2009	0.1
Portugal	2011-2013	1.3
India	2008-2009	0.19
USA	2015-2016	3.9

Several drugs are used to treat acute attacks of gout which includes Colchichine, Non steroidal anti inflammatory drugs (NSAIDs), and Corticosteroids. NSAIDs, especially Indomethacin, are the preferred first line choice of drugs. Oral NSAIDs can be given at maximal dose and continued for 2-3 days after relief of symptoms. Guidelines for dosing of NSAIDs include indomethacin 50 mg three-times daily, naproxen 500 mg twice daily, ibuprofen 600 mg three-times daily, or diclofenac 50 mg three-times daily, and possibly etoricoxib 120 mg once daily for a maximum of 1 week.

Several studies have compared the effectiveness of different NSAIDs and found similar clinical outcomes between Indomethacin and Etorcoxib. Colchicine is a most popular drug used in some countries like France for the gout attacks. Dose of 0.5mg every eight hours is found to be appropriate for patients whereas a high dose up to 6mg may cause toxicity in some patients. Corticosteroids are the alternative treatment choice for NSAIDs and colchicine intolerant patients. Intra-articular corticosteroids are given when the gout is limited to a single joint. There are different forms of corticosteroids available in the market such as oral, intramuscular, and intra-articular (eg: Prednisone 40mg, 20mg and 10mg respectively). Rebound flares are the common adverse reaction found after discontinuation of the drug. Once the symptoms has subsided by the use of NSAIDs or corticosteroids, the SUA concentration must be decreased to prevent gout attacks from recurring, Hence long term management of gout focuses on lowering SUA level to normal (<0.36mmol/L). There are two major classes of drugs used to reduce SUA levels,

Urate-lowering therapy (ULT), specifically Uricosuric drugs and Xanthine oxidase inhibitors (XOIs).

Uricosuric drugs such as Propenecid and Benzbromarone reduces the urate concentration by inhibiting the reabsorption of Uric acid mediated by the URAT-1. Probenecid is a URATE-1 inhibitor commonly prescribed in US, Canada and France. It is usually dosed 500-1000 mg twice a day and can be given as combination with XOIs when XOIs mono therapy is not effective. Benzbromarone 100mg/day is a long acting and well tolerated Uricosuric drug in 95% of the patients. it is found to be more effective than Allopurinol in reducing the severity and incidence of gout attacks and tophi. However, It has been proven to result in severe hepatic damage in patients and marketing of the drug was stopped in 2003 in some countries.

Renal and liver function tests, complete blood count and SUA levels should me measured every 3-4 weeks while titrating the dose as researchers have reported the association of hepatoxicity, elevated serum alkaline phosphatase, Allopurinol hypersensitivity syndrome, hepatocellular injury and acute kidney injury with Allopurinol use.

It is evident that gout with its unpredictable attacks characterized by severe pain , disability, and activity limitation have an enormous impact on the life of patients. Several studies have highlighted that the gout is affecting the patients physically, mentally, socially and financially , leading to compromised Health related quality of life. The World Health Organization has defined quality of life as "an individual's perception of life in the context of culture and value system in which he or she lives and in relation to his or her goals, expectations, standards and concerns".

Measures of Health Related Quality of Life (HRQOL) help us to analyze the extent of the effect of a disease on a patient's life as well as the effectiveness of the health care interventions given to the patients. There are different instruments available to assess the HRQOL which include, 36-Item Short Form Health Survey (SF-36) , Short Form-12 (SF-12), and Health Assessment Questionnaire-disability index (HAQ-DI). The SF-36 is a popular questionnaire used to assess HRQOL of patients. It includes 36 questions from 8 different scales to measure physical as well as mental health.

Even though febuxostat has proven to be more efficacious than Allopurinol in higher doses, it is also responsible for causing several side effects on prolonged use in patients. Hence, it is necessary to conduct more studies emphasizing the safety and efficacy of Febuxostat over Allopurinol. As the gout is a serious illness affecting HRQOL of patients, there is a need to encourage interventions inorder to improve their QOL.

MATERIALS AND METHODS

Study Design: This is a community based Cross-sectional study (prospective).

Study Duration

- Planning: 1 month
- Data Collection: 3 months
- Data Interpretation: 1 month
- Thesis: Writing: 1 month

Study Centre: The study was conducted at selected orthopaedic clinics in T. Dasarahalli, Bengaluru District

Sample Size: A total of 73 subjects were collected out of which 50 patients were selected for the study.

Inclusion Criteria

- Patient diagnosed with gout
- Patients above 18 years of age.
- Patients prescribed with either Allopurinol or Febuxostat.

Exclusion Criteria

- Those who are not willing to participate
- Pregnant and lactating women
- Other Rheumatologic/ Muscular disorder.

Source of Data

The different sources of data were: One to one interview with study subject and Questionnaires

RESULTS

This study was conducted in selected orthopaedic clinics in T. Dasarahalli, Bengaluru District. It was carried out for a period of 6 months, and 50 samples were collected. Among the 50 samples included, 25 samples were on Allopurinol and the other 25 samples were on febuxostat.

Age Distribution of Subjects in Febuxostat Group

The mean age of the study population was found to be 48.96 ± 9.25 years. Age group 40-50 years were in majority accounting for 48% of the total population and age group 62-72 were minimal in number i.e. 12%.

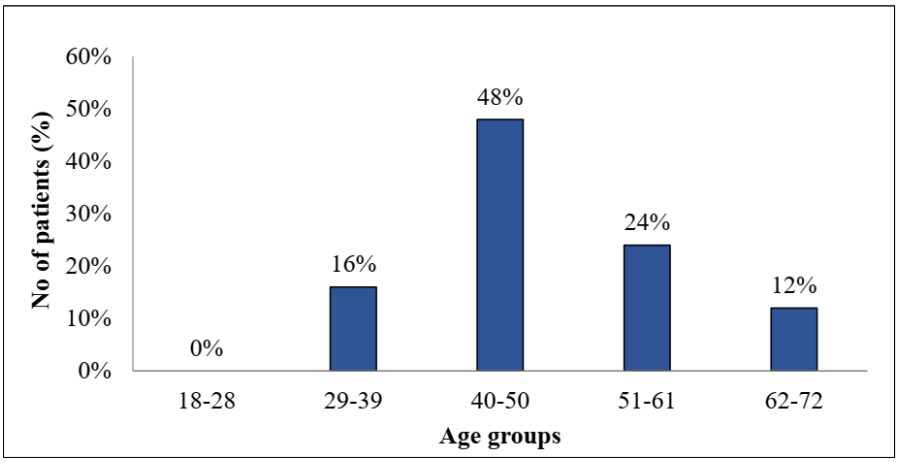

Figure 2: Age distribution of subjects in Febuxostat group

Dose Distribution among Subjects in Febuxostat Group

Out of 25 samples, 16 of them were taking 40mg Febuxostat (64% of the population) and 9 were taking 80mg Febuxostat (36% of the population) as shown below.

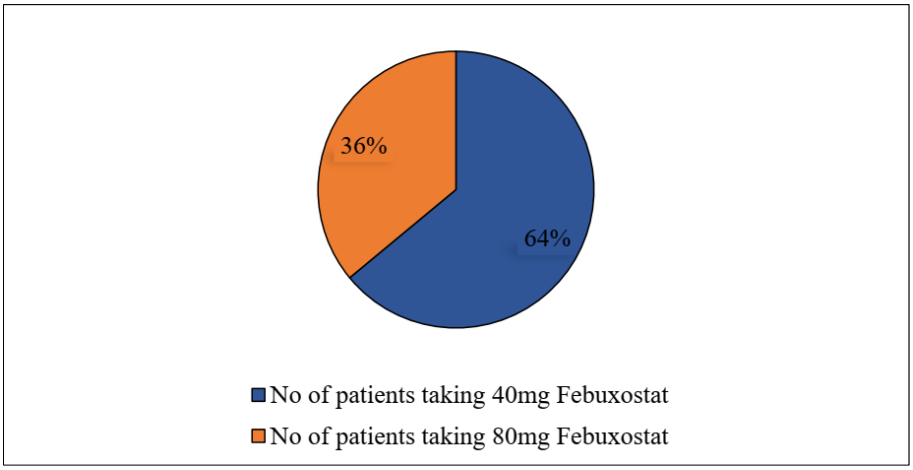

Figure 3: Dose distribution among Febuxostat subjects

Age Distribution of Subjects in Allopurinol Group

The mean age of the study population was found to be 50.72±7.6 years. Age group 51-61 years were in majority accounting for 48% of the total population and age group 62-72 were minimal i.e. 4%

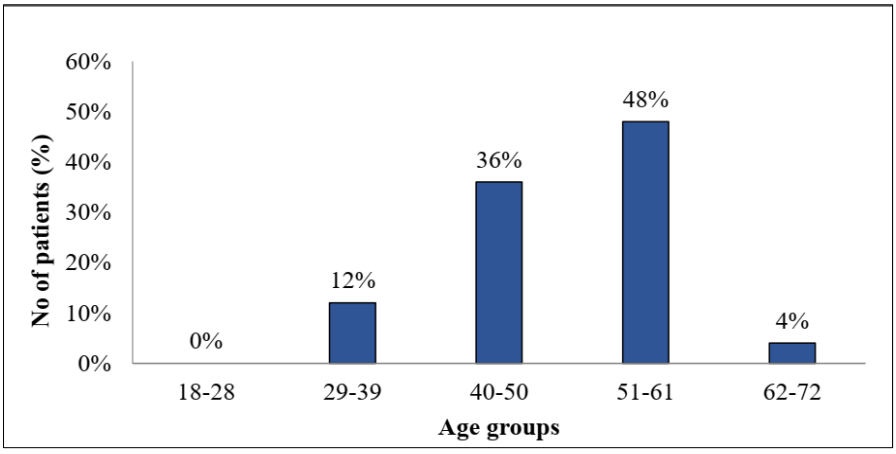

Figure 4: Age distribution of subjects in Allopurinol group

Dose Distribution among Subjects in Allopurinol Group

Out of 25 samples, 13 of them were taking Allopurinol 100mg (52%), 10 of them were taking 200mg (40%) and 2 of them were taking 300mg (8%) once daily.

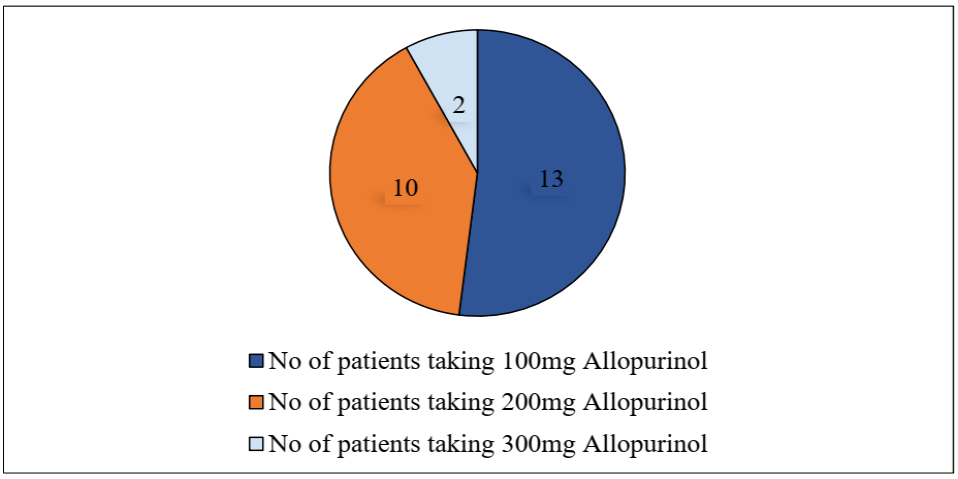

Figure 5: Dose distribution among Allopurinol subjects

Assessment of Safety and Effectiveness in Febuxostat and Allopurinol Group

Assessment of Effectiveness in Febuxostat Subjects

Febuxostat 40mg was administered by 64% and 80mg was administered by 36% of the total febuxostat population. By assessing the Uric Acid levels in both groups, Febuxostat 40mg ($p < 0.05$) was found to be more effective compared to the other.

Table 2: Comparison of SUA levels between Febuxostat 40 and 80mg

FEBUXOSTAT		
	40mg	80mg
Number of patients	16	09
Initial		
Mean	6.78	7.63
Standard deviation	1.00	0.75
Range	4.20 - 8.20	6.00 – 8.30
After 3 months		
Mean	5.80	6.43
Standard deviation	0.83	1.09
Range	4.30 – 7.50	4.20 – 7.40
P value	.001	.0002

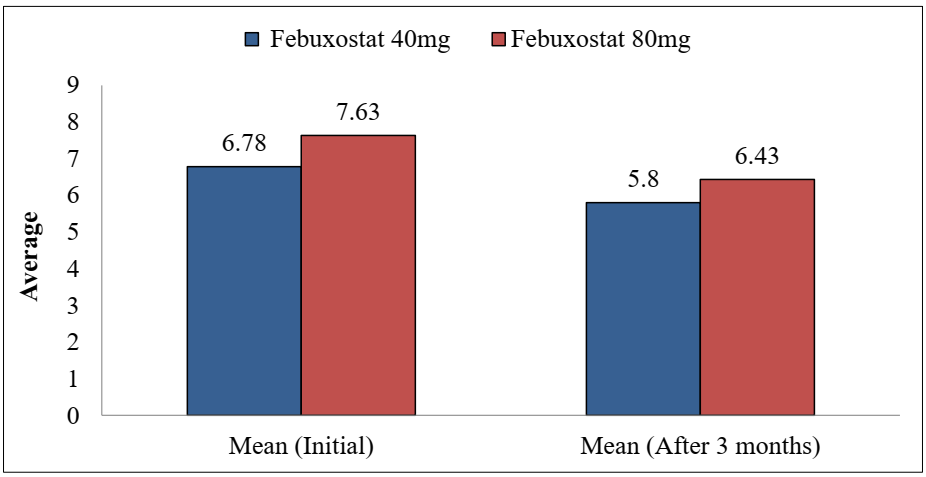

Figure 6: Comparison of mean values of SUA levels in Febuxostat subjects

Assessment of Effectiveness in Allopurinol Subjects

Allopurinol 100mg, 200mg and 300mg were administered by 52%, 40% and 8% of the total population respectively. It was found that allopurinol 200mg (p = 0.05) reduced the Uric Acid levels much faster than Allopurinol 100mg.

Table 3: Comparison of SUA levels between Allopurinol 100 and 200mg

ALLOPURINOL		
	100mg	200mg
Number of patients	13	10
Initial		
Mean	7.40	6.69
Standard deviation	0.93	0.98
Range	5.50 – 8.30	5.50 – 8.30
After 3 months		
Mean	7.17	6.07
Standard deviation	0.80	0.85
Range	5.10 – 8.10	4.90 – 8.00
P value	> 0.05	.05

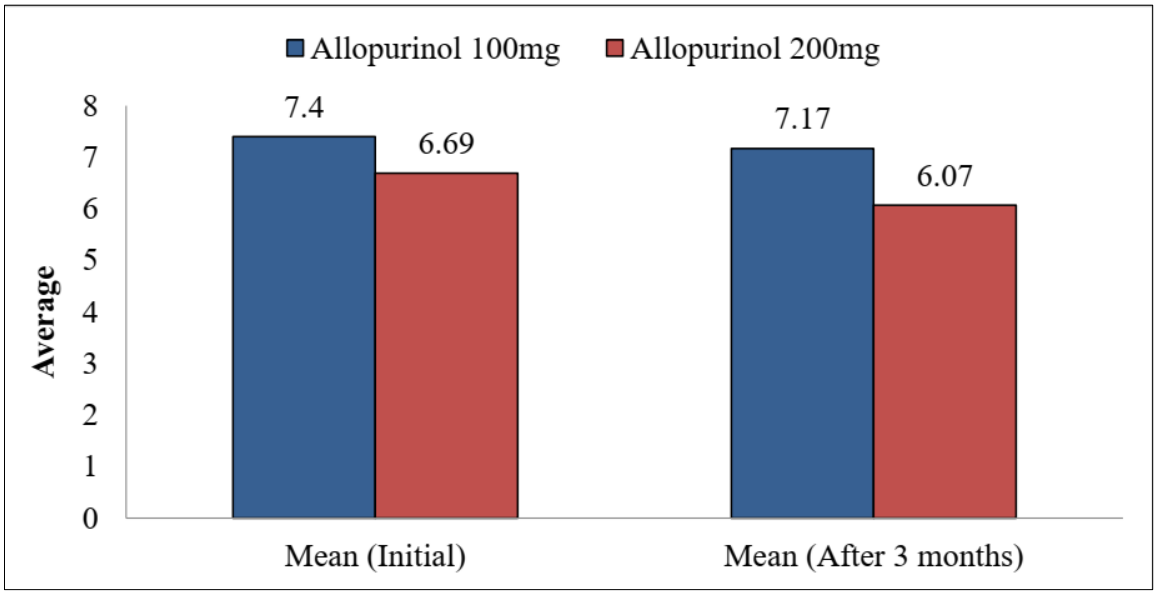

Figure 7: Comparison of mean values of SUA levels in Allopurinol subjects

Comparison of Effectiveness between Allopurinol and Febuxostat Group

A total of 50 samples were included in this study and the number of subjects were equally distributed in both groups as 25 samples (50%) in febuxostat and 25 samples (50%) in allopurinol group. On comparing the effectiveness of these drugs, febuxostat was found to lower the Uric acid level much faster than allopurinol owing to its greater effectiveness.

Table 4: Comparison of SUA levels between Febuxostat and Allopurinol group

	FEBUXOSTAT	ALLOPURINOL
Number of patients	25	25
Initial		
Mean	7.09	6.96
Standard deviation	0.99	1.11
Range	4.20 – 8.30	4.30 – 8.30
After 3 months		
Mean	6.03	6.58
Standard deviation	0.96	1.04
Range	4.20 – 7.50	4.50 – 8.10

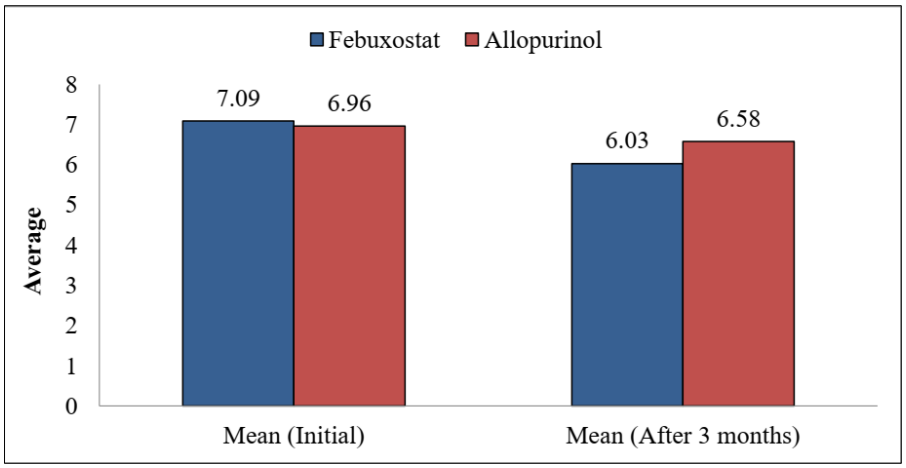

Figure 8: Comparison of mean values of SUA levels between Febuxostat and Allopurinol

Assessment of Safety in Febuxostat Subjects

Safety of the drug was assessed by analyzing side effects associated with the treatment and it was found that gastrointestinal disturbances, increased blood pressure, joint pain were the common side effects seen in 24%, 16% and 12% of the population respectively. Gout attack was the least common side effect noticed in subjects, which was found to be 4%.

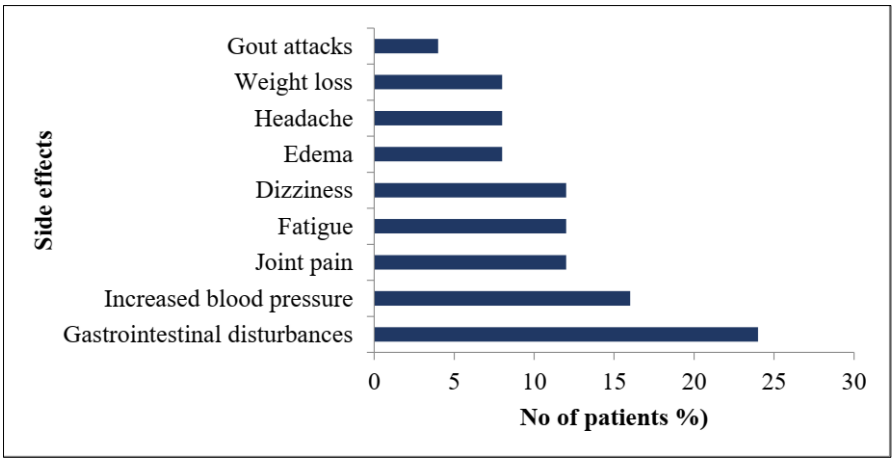

Figure 9: List of noticed side effects in Febuxostat subjects

Assessment of Safety in Allopurinol Subjects

The common side effects associated with the treatment were gastrointestinal disturbances (28%), joint pain (16%), weight loss (12%) and loss of appetite (12%). The least common side effects noticed were drowsiness (4%) and dizziness (4%).

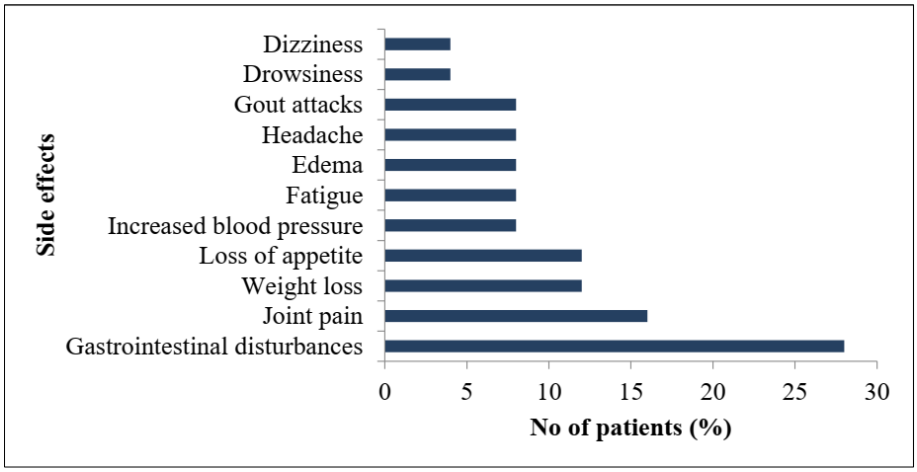

Figure 10: List of noticed side effects in Allopurinol subjects

Effect of Febuxostat on Serum Creatinine

Febuxostat 40mg ($p < 0.05$) was found to show better pharmacokinetic mechanism on subjects as this was inferred from the Creatinine levels obtained from the samples owing to its better safety than febuxostat 80mg ($p < 0.05$). Febuxostat 40mg and 80mg were administered by 64% and 36% of the study population respectively as depicted in below table.

Table 5: Comparison of SCr levels between Febuxostat 40 and 80mg

FEBUXOSTAT		
	40mg	80mg
Number of patients	16	09
Initial		
Mean	1.01	1.34
Standard deviation	0.43	0.91
Range	0.60 – 2.40	0.40 – 3.10
After 3 months		
Mean	0.88	1.18
Standard deviation	0.41	0.91
Range	0.40 – 2.00	0.30 – 2.80
P value	.005	.008

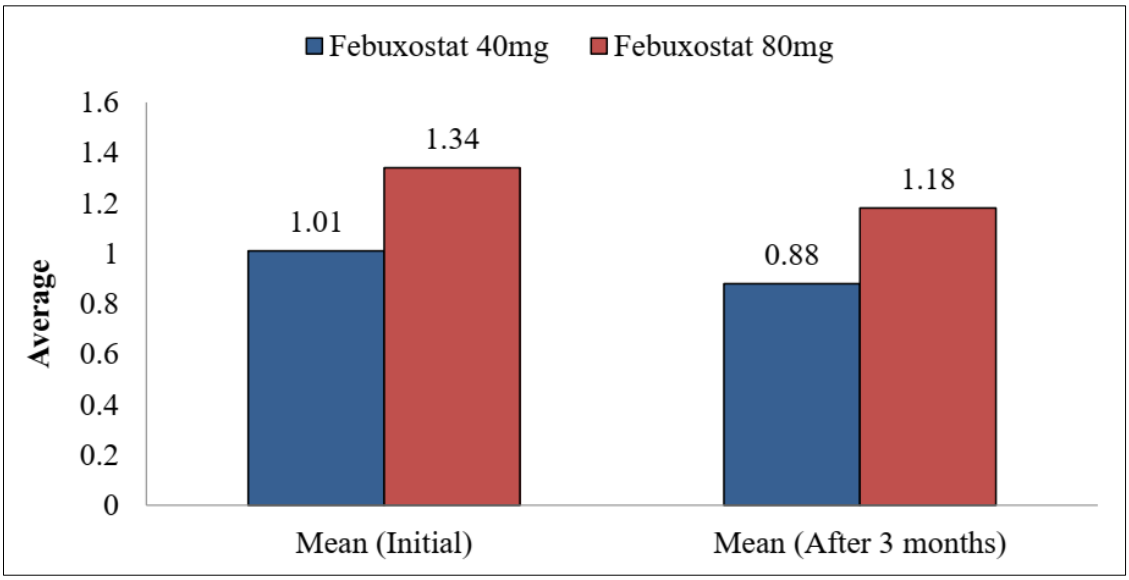

Figure 11: Comparison of mean values of SCr levels in Febuxostat subjects

Effect of Allopurinol on Serum Creatinine

Figure illustrates that number of subjects belonging to allopurinol 100mg and 200mg were 13 (52%) and 10 (40%) respectively. It was found that allopurinol 100mg had better pharmacokinetic mechanism on subjects.

Table 6: Comparison of SCr levels between Allopurinol 100 and 200mg

ALLOPURINOL		
	100mg	200mg
Number of patients	13	10
Initial		
Mean	1.376	1.37
Standard deviation	0.73	0.45
Range	0.40 – 2.90	1.00 – 2.20
After 3 months		
Mean	1.276	1.34
Standard deviation	0.696	0.629
Range	0.50 – 3.00	0.50 – 2.50
P value	> 0.05	> 0.05

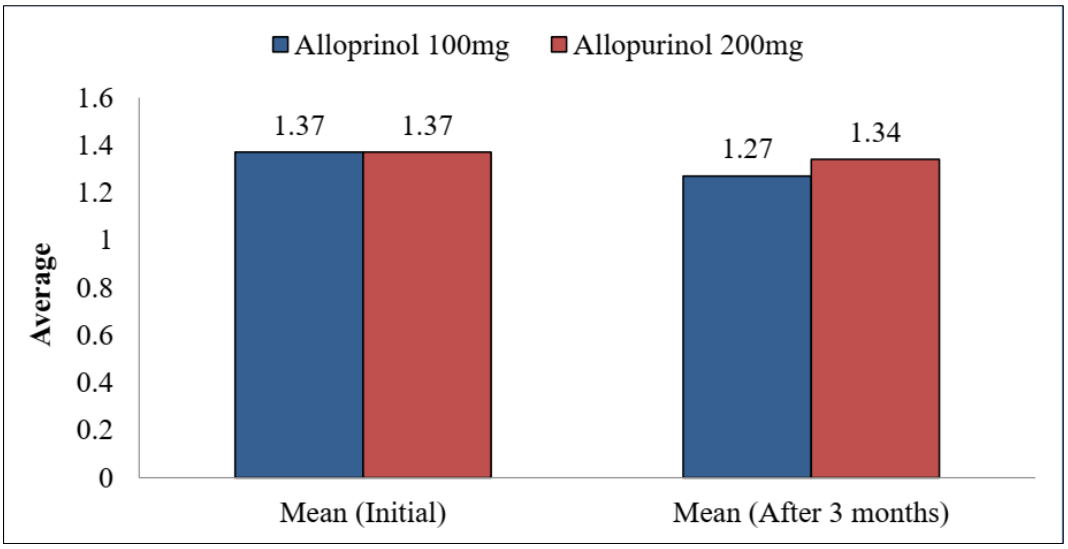

Figure 12: Comparison of mean values of SCr levels in Allopurinol subjects

Comparison of Effect of Allopurinol and Febuxostat on Creatinine

A total of 50 samples were included in the study and both allopurinol and febuxostat group had 25 samples each. On comparing the effect of these drugs on Creatinine, it was found that subjects belonging to febuxostat had better Pharmacokinetic mechanism compared to subjects taking allopurinol.

Table 7: Comparison of SCr levels between Febuxostat and Allopurinol group

	FEBUXOSTAT	ALLOPURINOL
Number of patients	25	25
Initial		
Mean	1.13	1.32
Standard deviation	0.65	0.61
Range	0.40 – 3.10	0.40 – 2.90
After 3 months		
Mean	0.99	1.26
Standard deviation	0.63	0.64
Range	0.30 – 2.80	0.50 – 3.00

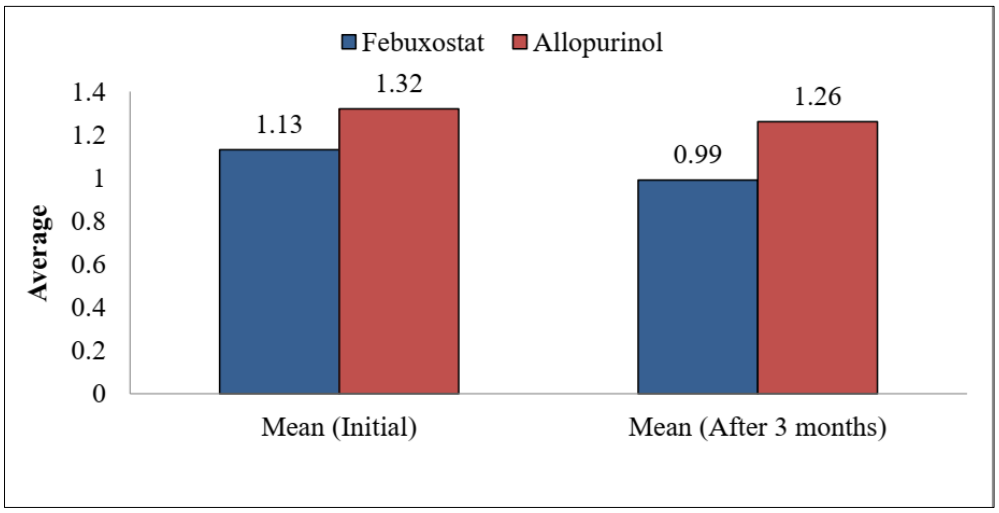

Figure 13: Comparison of mean values of SCr levels between Febuxostat and Allopurinol

Health Related Quality of Life Assessment

Average of PCS and MCS in Febuxostat Group

The total average of four domains each under PCS and MCS was found to be 41.825 and 62.775 respectively. The overall average of both PCS and MCS was 52.3.

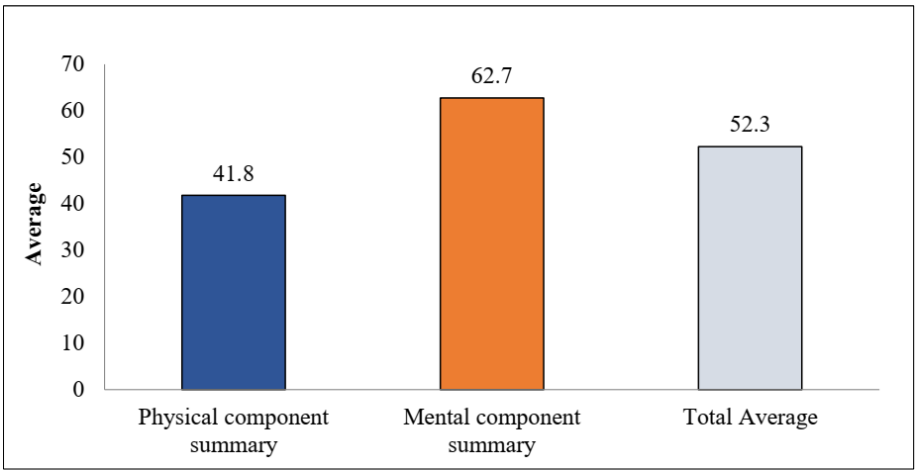

Figure 14: Physical and mental component summary of Febuxostat

Average of PCS and MCS in Allopurinol Group

The total average of four domains each under PCS and MCS was found to be 42.825 and 61.385 respectively. The overall average of both PCS and MCS was 52.1.

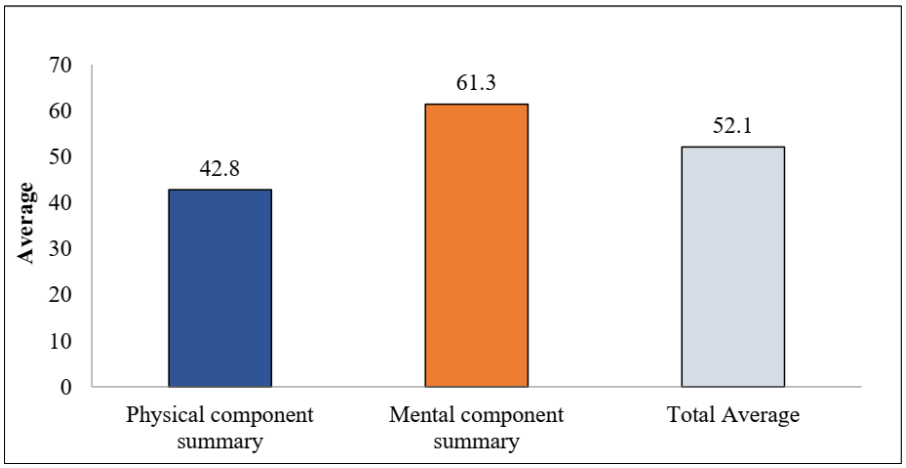

Figure 15: Physical and mental component summary of Allopurinol

Overall Comparison of HRQOL in Febuxostat and Allopurinol Group

On comparing the QOL scores in both Febuxostat and Allopurinol group, it was found that the subjects belonging to the Febuxostat group had the highest overall mean score i.e. 52.3 when compared to overall mean score of Allopurinol group i.e. 52.1

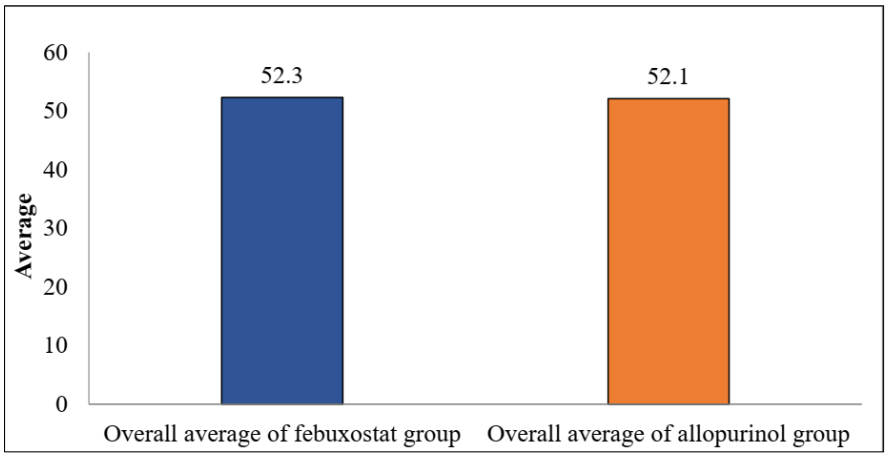

Figure 16: HRQOL of Febuxostat and Allopurinol subjects

DISCUSSION

This study was a 6-month long observational study conducted in selected orthopedic clinics in T. Dasarahalli, Bengaluru District. A total of 50 subjects were enrolled in the study based on inclusion and exclusion criteria. Of 50 subjects, the number of subjects in both Febuxostat and allopurinol were equally distributed. All the subjects included in this study were males and the mean age of the subjects was 49.84. This study conducted in subjects with gout, compared treatment with Febuxostat and allopurinol with regard to their safety and Urate-lowering efficacy. Both allopurinol and Febuxostat administration resulted in sustained reduction in SUA levels in subjects. Our primary outcome of the study was based on the proportion of participants reducing SUA to less than or equal to 6.0mg/dL similar to a study conducted by Becker MA *et al*., In this study we found that a higher proportion of patients were receiving Febuxostat 40mg (64%) and it was found to reduce SUA to a great extent. This result was obtained from the comparison of mean values (initial and after three months) of SUA levels in Febuxostat 40mg population. Whereas 36% of Febuxostat group were taking 80mg of the drug and the levels of SUA were also found to be reduced after 3 months of the treatment. Our study had limitation in the time period and study samples owing to the restriction in drug dose comparison. In a study conducted by Graham G G *et al.,* showed 40% and 50% reduction in SUA levels by the use of allopurinol 100mg and 200mg respectively. Similarly, allopurinol 200mg was found to reduce SUA much faster than 100mg of allopurinol in this study. Comparison of the effectiveness of both Febuxostat and allopurinol in the study revealed that Febuxostat had better effectiveness as it reduced SUA levels faster than allopurinol in three months. It was obtained from the comparison of mean values of UA levels (initial and after 3 months) in both Febuxostat and allopurinol group, which was found to be 6.03 ± 0.96 and 6.58 ± 1.04 respectively. In a similar study conducted by Javinder S *et al.*, found the mean values of SUA levels to be 6.4 ± 2.0 and 6.6 ± 1.7 in Febuxostat and allopurinol group respectively. In this study the safety of these drugs were also assessed by analyzing side effects occurred during the treatment. However, the results couldn't be concluded due to the lack of information regarding the presence of comorbidities and intake of other drugs, which could heavily influence the side effects experienced by the participants. In this study the effect of these drugs on SCr was also assessed, as gout is a metabolic disease affecting renal function. Our findings were similar to the study conducted by Javinder S *et al.*, it was found that SCr has decreased in both Febuxostat and allopurinol group. Comparison of both these drugs on SCr levels manifested that Febuxostat had better pharmacokinetics when compared to allopurinol. Our conclusion was based on the comparison of mean values of SCr levels of both Febuxostat and allopurinol group, which was found to be 0.99 and 1.26 respectively.

The HRQOL was assessed using SF-36 questionnaire, and according to the results of the study the scores for physical functioning, role limitation due to physical health, pain and general health of both Febuxostat and allopurinol group was 66.6, 18, 49.3, 33.4, and 66.2, 22, 50.1 and 33 respectively. While scores of mental components including social functioning, role limitation due to emotional problems, energy and emotional wellbeing was found to be 74, 29.3, 68.4, 79.4, and 75.5, 20, 71.8, 78.2, in febuxostat and allopurinol group respectively. Mental health status was not highly affected in our study subjects which is in line with the study conducted by Susan J L *et al.*, Gout can have impact on physical functioning due to pain associated with the disease. This study showed that the subjects were forced to reduce the amount of time they spend on activities at work due to their compromised health. Also, both the groups had difficulty in performing vigorous activities like running, lifting heavy objects, climbing several flights of stairs etc. Whereas the mean scores for mental components such as social functioning, energy and role limitation due to emotional problems was found to be the lowest in both groups. On comparison of QOL scores of both Febuxostat and allopurinol group it was found that there was no significant difference between the mean values of overall HRQOL in both groups. The average PCS and MCS scores of Febuxostat group was found to be 41.8 and 62.7 indicating an average HRQOL as 52.3. Similarly, average scores for PCS and MCS in allopurinol group was found to be 42.8 and 61.3 indicating an average HRQOL as 52.1. Our findings were similar to the study conducted by Susan J L *et al.*, indicated that gout patients have a compromised HRQOL in both physical and mental domains.

CONCLUSION

Gout is the most prevalent form of inflammatory arthritis, which arises due to the elevated levels of SUA, primarily affecting the joints. Global burden of gout has risen in recent decades, making it a national health concern. The aim of the study was to compare the safety and effectiveness of Allopurinol and Febuxostat in gout patients and we observed that Febuxostat was more effective than Allopurinol when comparing the ability to achieve target SUA. Both the drugs were found to be safe on renal profile as they were capable of maintaining acceptable SCr levels. The results of the current study indicate that Gout had a significant impact on different aspects of HRQOL, which could be because of the pain associated with the disease and Febuxostat subjects tends to have better QOL. These results suggest that gout can be more effectively managed with the drug Febuxostat than Allopurinol. Findings of our study can inform patients and physicians when they are making a choice regarding the treatment of Gout. Treatment strategies to improve disease control may also lead to improvements in productivity and HRQOL of patients.

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