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# "COMPARISON OF URATE-LOWERING EFFICACY AND SAFETY OF FEBUXOSTAT AND ALLOPURINOL IN GOUT PATIENTS"

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## ABSTRACT
Gout is a disorder that manifests as a spectrum of clinical and pathologic features build on a foundation of an excess body burden of uric acid, manifested in part by hyperuricemia, which is variably defined as a serum urate level greater than either 6.8 or 7.0 mg/dl. Gout can also manifest as chronic arthritis of 1 or more joints. Gout is common inflammatory arthritis associated with important co-morbidities including hypertension, renal impairment, cardiovascular disease, obesity and type 2 diabetes. Age, gender, genetic and race-related risks, diet (especially purine rich food) and some medications (thiazide, loop diuretics, ACE inhibitors, and beta blockers) have been found as increased risk factors for development of gout. Gout develops in men more than women and seldom occurs in premenopausal women. Uricostatic drugs (Xanthine oxidase inhibitors) are widely used in treating chronic gout. This study aimed to compare the efficacy of two uric acid lowering drugs (Febuxostat and Allopurinol) for providing symptomatic pain relief and improving the functional state of the patients. Treatment of gout with Febuxostat and Allopurinol appears to be clinically effective in decreasing uric acid and providing symptomatic and functional relief in the patients. In the view of statistical data, we consider that febuxostat may be the first choice if early considerable symptomatic improvement is required.

**KEYWORDS**: Febuxostat, Allopurinol, Gout, Hyperuricemia, Xanthine Oxidase

## INTRODUCTION
Gout is a form of arthritis with a documented history spanning several thousands of years. Observed by the ancient Egyptian medical practitioner Imhotep as early as 2640BCE [40], it was also described several centuries later by the Greek physician Hippocrates (400BCE), the father of modern medicine, who referred to it as podagra, or "the unwalkable disease".[1]Tissue deposition of monosodium urate monohydrate crystals in supersaturated extracellular fluids of the joints, and certain other sites, mediates most of the clinical and pathologic features of gout. Typically, the disease initially presents as acute episodic arthritis.Tophi, mainly found in articular, peri-articular, bursal, bone, auricular and cutaneous tissues, are a pathognomonic features of gout. Renal manifestations of gout include urolithiasis, uratenephropathy.[2]Gout was described by Hippocrates as "the disease of kings" due to its association with rich diet[3] known risk factors for gout include high dietary purine consumption, e.g. seafood, various types of meat, and certain vegetables, as well as alcohol intake, obesity, and the use of particular drugs such as diuretics and low dose aspirin.[4, 5]The greatest predictor of gout risk and development is the concentration of uric acid in the serum. Uric acid levels commonly fall into the

range of 2.4 - 6.0 mg/dL in women and 3.4 - 7.0mg/dL in men.[6]A prime risk factor in gout is gender. Gout is the most common form of inflammatory arthritis in men over 40.Gout often occurs in the presence of other conditions, such ashypertension, renal impairment, diabetes mellitus and cardiovascular disease.

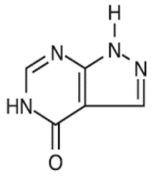
Incidence of gout in India is not very clear. The prevalence is 0.12% as per International League of Nations against Rheumatism, Community Oriented Program for Control of Rheumatic Diseases (ILAR COPCORD) study in Bhigwan village of India.A study from Vellore revealed that 15.8% of the affected patients are less than 30 years of age; urban Indian population is involved more than the rural population and due to increased prevalence of metabolic syndrome in younger population, the first attack of gout occurs a decade earlier to them.[7]Another Indian study showed that high uric acid level is associated with laboratory and anthropometric parameters of metabolic syndrome.[8]

There are four stages of gout, first is Asymptomatic Hyperuricemia. Elevated levels of urate are present within the body, but the individual does not display symptoms clinically.**Stage 2**, an **acute gout attack** or flare, comprises of the buildup and small deposits of monosodium urate crystals in and around specific joint spaces. Characteristically, the patient may suffer pain, redness, swelling, and warmth, which may last for lengths of time ranging from days to weeks. **Stage 3, Intercritical Gout** occurs in a patient who had prior gout flares, which have successfully subsided and who has no current expression of gout symptoms. A patient may report normal joint function, though hyperuricemia continues to occur with an increasingly greater possibility for damage in tissues due to continued deposition of urate crystals.The **final stage** of progression, **Chronic Gout**, is typified by a resulting destructive and disabling inflammatory process causing ongoing pain and aching of the joint(s). Chronic tophaceous arthritis is a product of the continuous deposition of urate crystals around and within the joint space. In multiple cases, deformities and destruction of the bone and joints involved have occurred, causing a reduction in quality of life due to the damage and pain.

Diagnosis of gout includes joint aspiration and synovial fluid analysis, serum uric acid measurement, 24 hour urinary uric acid evaluation, blood studies (including white blood cells, triglyceride, high density lipoprotein, glucose and renal and liver function tests).

The **gold standard for the diagnosis**of acute gout is the demonstration of strongly negative birefringent needle and rod-shaped crystals of MSU in the synovial fluid under compensated polarizing light microscopy.**American College of Rheumatology Criteria for the Classification of Acute Arthritis for Primary Gout** (Wallace et al., 1977) is used to confirm the diagnosis of gout.[9]

The main therapeutic agents for the treatment of **acute attacks** are colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. The American College of Rheumatology guidelines recommend either allopurinol or febuxostat as first line therapy; however, third-party payers often stipulate allopurinol use first due to the substantial cost difference.[2]**Colchicin**e is the ideal drug in patients where the diagnosis of gout is not confirmed. It acts by inhibiting the action of neutrophils.[10] **Chronic gout** is treated with urate lowering drugs. About 1/3rd of patients with anattack of gout have a second attack within one year. So it is imperative to have prophylactic use of urate lowering drugs. Uricostaticdrugs (xanthine oxidase inhibitor) such as Allopurinol and febuxostat.

XANTHINE OXIDASE 


**Allopurinol** is non selective xanthine oxidase (XO) inhibitor that decreases acute gout attack incidence by decreasing the amount of serum uric acid through the inhibition of xanthine oxidase enzyme, which is involved in uric acid synthesis. It acts on purine catabolism, without disrupting the

biosynthesis of purines. It is a commonly prescribed urocostatic pro drug that is converted in the liver to the active metabolite oxypurinol.[11]

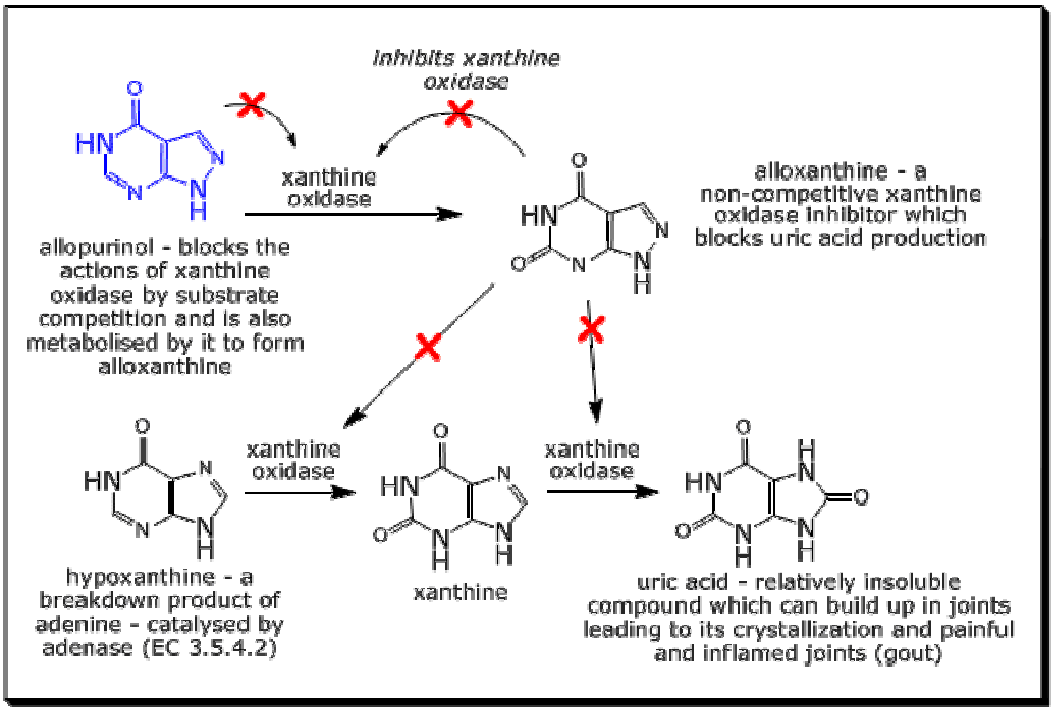
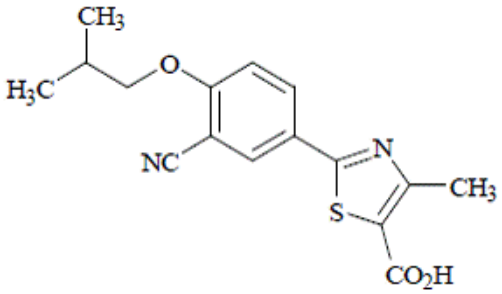



**Figure.Steps catalysed by xanthine oxidase (XO) in the breakdown of purines into uric acid.** The figure shows the steps that are inhibited by oxypurinol. (Adaptedfrom Pacher et al., 2006).

**Febuxostat**, is a non-purine analogue XO inhibitor. The FDA approved Febuxostat in February 2009.It inhibits boththe reduced and oxidized forms of the enzyme in contrast to allopurinol.Febuxostat is a non-purine analogue, and thus does not block the other metabolites of purine and have no effect on pyrimidine metabolism. All these help to alleviate allopurinol toxicities. Another advantage is its effectiveness in mild to moderate renal failure. Major side effects include rash, elevated liver enzymes, diarrhoea and non-specific arthralgia's. There is lesser drug interaction with azathioprine, 6-mercaptopurine and theophylline.

The present study aimed to compare the efficacy of two urate lowering drugs (Allopurinol and Febuxostat) for providing symptomatic pain relief and improving the functional state of the patients having gout. Moreover, there is very less data available on the comparison of two drugs using VAS scale, further divided into three parts namely subject's assessment of pain (SAP), subject's assessment of disease activity (SAD) and physician's assessment of disease activity (PAD). So we planned the study to get adequate data on Indian population in terms of efficacy, safety, duration of action and reduction in serum uric acid level in gout patients with the use of these two drugs.



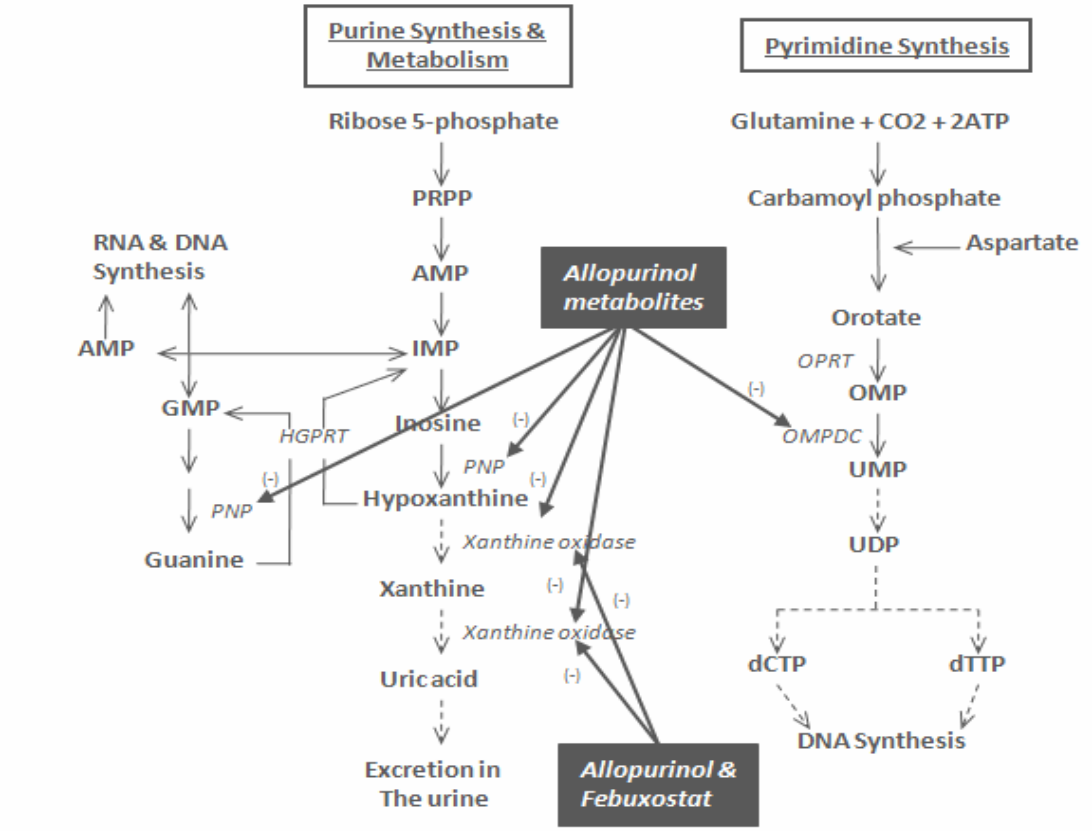




Figure 1. Mechanisms of action of allopurinol and febuxostat in gout.

*AMP = adenosine monophosphate; dCTP = deoxycytidine triphosphate; dTTP = deoxythymidine triphosphate; GMP = guanosine monophosphate; HGPRT = hypoxanthine-guanine phosphoribosyltransferase; IMP = inosine monophosphate; OMP = orotate monophosphate; OMPDC = Orotidine-5'-monophosphate decarboxylase; OPRT = Orotate phosphorisbosyltransferase; PNP = purine nucleoside phosphorylase; UMP = uridine monophosphate; UDP = uridine diphosphate*

## EXPERIMENTAL SECTION

### MATERIALS AND METHODS

The study was conducted at Department Of Orthopedics, Nova Specialty Hospitals, Kailash Colony, New Delhi during the period from Feb 2014 to June 2014. A retrospective, single blind, randomized,

comparative model was designed for the study.Both male and female patients with 30-75 years of age, serum uric acid ≥8.0 mg/dl (hyperuricemia) who are not under treatment with any uric-acid lowering drugs, who met the American college of rheumatology criteria for diagnosis of gout, presence of Monosodium urate monohydrate microcrystals in joint fluid, a self-reported history of ≥ 2 gout flares in the year prior to initial screening visits, patients who are allowed to be on urate lowering therapy and who agreed to sign the informed consent were included in the study. Patients with secondary hyperuricemia, xanthinuria, previous history of hypersensitivity to NSAIDs, colchicine, allopurinol and febuxostat , who had gout attack in last two weeks, patients with aspirin-induced asthma, peptic ulcer, serious hematological disorder, uncontrolled diabetes, who require dialysis, and who are being treated with any systemic immunosuppressant were excluded from the study.

A retrospective, single blind, randomized, comparative model was designed for the study. A total number of 65 patients were assessed for the study. Each patient was followed up for 1 year. The retrospective data was taken at the baseline, at the $4^{th}$ month, then at $8^{th}$ month and then at final follow-up. The study was done during the period from Feb 2014 to June 2014.The patient was asked about the frequency of the gout flare. The patient was asked to fill the subject's assessment of pain (SAP) visual analogue scale and a subject's assessment of disease activity (SAD) visual analogue scale (VAS) at their follow up. A physician performed a complete physical examination (swelling, tenderness, and redness, no. of tophi, frequency of gout flares) on each patient and completed a subject's assessment of disease activity (PAD) visual analogue scale. The primary outcome measures in this study were flare characteristics (tender joints, swollen joints, patient global assessment). Serum uric acid level was also analyzed at baseline and at each visit.

**ASSESSMENT CRITERIA**: A total of score obtained after scoring by the patients and physician was calculated by adding individual scores of visual analogue scale (SAP, SAD, PAD) at each visit and the total score generated was considered as the final value which was then assessed according to the statistical analyses.

**STATISTICAL ANALYSIS**

The software used for the statistical analysis was **SPSS (statistical package for social sciences) version 16.0 and Epi-info version 3.0**. The values were represented in **Number (n), Percentage (%) and Mean (υ).**The statistical tests used were **Unpaired or independent samples t-test** for comparison of mean value of 2 groups.The **p-value** was taken significant when less than 0.05 **($p<0.05$)** andConfidence interval of 95% was taken.

**OBSERVATION AND RESULT**

A total of 65 subjects were assessed from February 2014 to March 2014.Eleven subjects were excluded as they did not meet inclusion criteria or fell in the exclusion criteria. One subject did not give consent for enrollment in the study and three patients did not come back for their follow up visits.

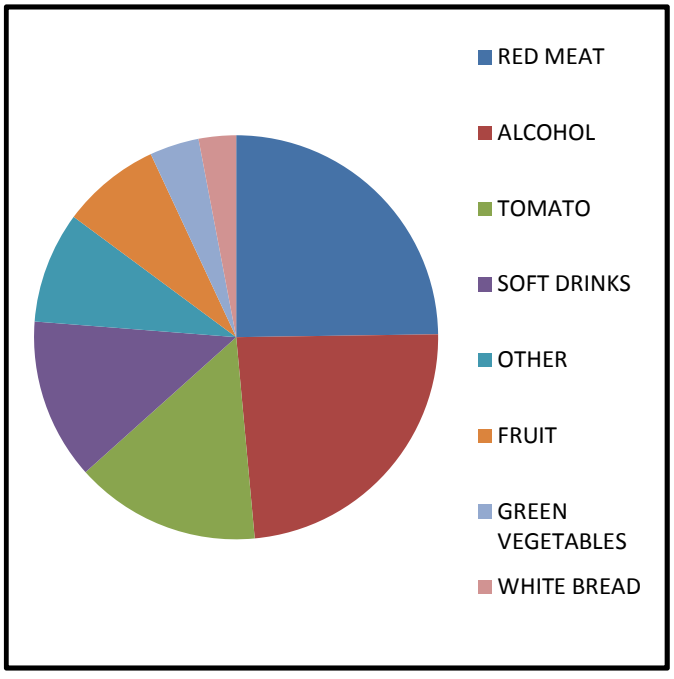
The remaining 50 subjects completed the study with 25 in Allopurinol group and 25 in Febuxostat group. None of the subjects enrolled suffered from serious adverse event. All the 50 subjects completed the efficacy analysis

**Baseline demography of study groups**

| | MEAN | | Standard deviation | | P value |
|---|---|---|---|---|---|
| | Allopurinol | Febuxostat | Allopurinol | Febuxostat | |
| Age(yrs) | 53.8 | 59.72 | 9.51 | 11.94 | **.239>.05** accept null hypothesis |
| Sex | 1.36 | 1.4 | .49 | .50 | **.574>.05** accept null hypothesis |
| Weight(Kg) | 72.6 | 73.52 | 7.31 | 10.63 | **.2>.05** accept null hypothesis |
| Height(m) | 1.62 | 1.66 | .08 | .07 | **.72>.05** accept null hypothesis |
| BMI($Kg/m^2$) | 27.88 | 28.13 | 0.69 | 1.01 | **.96>.05** accept null hypothesis |

Since in all the above cases , our p value is greater than 0.05 therefore we accept Ho(null hypothesis), i.e., there's no significant difference between the two study groups with respect to age, height, sex, weight and BMI. It means that the two sample **groups are homogeneous.**

**POTENTIAL DIETARY TRIGGERS FOR ACUTE ATTACKS**



**Baseline assessment scores using various scales**

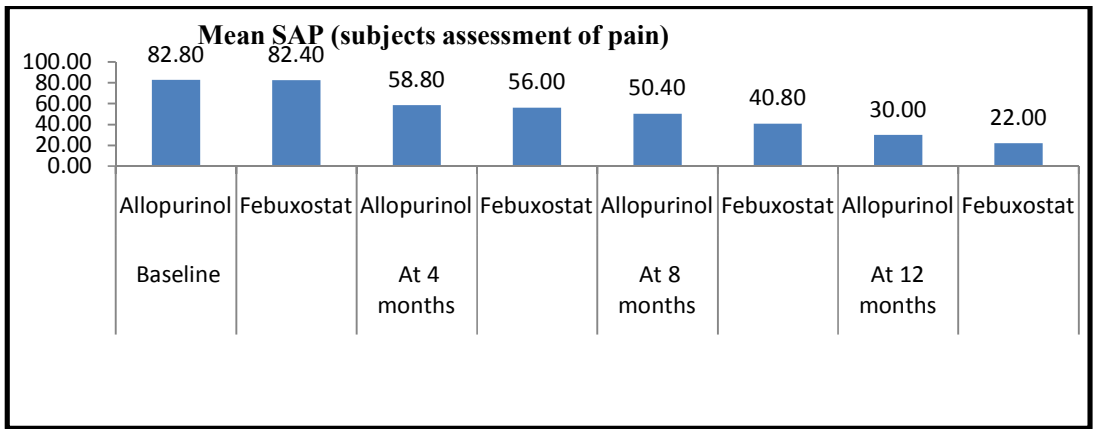
| | ALLOPURINOL/ FEBUXOSTAT | | ALLOPURINOL/ FEBUXOSTAT | | |
|---|---|---|---|---|---|
| | MEAN | | STANDARD DEVIATION | | P Value |
| **VAS** | | | | | |
| **SAP (subjects assessment of pain)** | 82.80 | 82.40 | 7.37 | 7.23 | 0.847**>.05** accept null hypothesis |
| **SAD (subjects assessment of disease activity)** | 84.00 | 81.60 | 5.00 | 5.54 | 0.114**>.05** accept null hypothesis |
| **PAD (physicians assessment of disease activity)** | 82.00 | 84.00 | 7.64 | 8.17 | 0.376**> .05** accept null hypothesis |
| **SERUM URIC ACID LEVEL** | 9.13 | 9.24 | 0.45 | 0.64 | 0.489**>.05** accept null hypothesis |
| **NO. OF TOPHI** | 4.20 | 4.40 | 0.76 | 0.50 | 0.279**>.05** accept null hypothesis |
| **GOUT FLARES** | 4.60 | 4.80 | 0.50 | 0.41 | 0.128**>.05** accept null hypothesis |

**EFFICACY END POINTS**

**Primary END-POINT: SAP (subjects assessment of pain) after 20 meters walk**

**SAP (subject's assessment of pain)** was taken at baseline and after every 4 months interval for 12 months. No statistical significant difference was observed at the baseline score as well as at the end of 4 months. But there was statistical significant difference when inter group comparison was done between the two groups at the end of 8 months and 12 months.

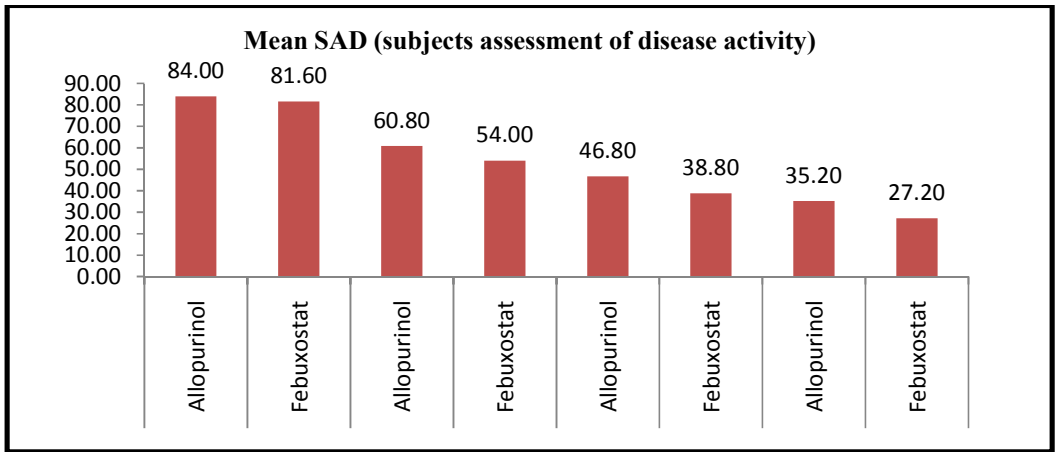
| SAP (subjects assessment of pain) | Drug group | Mean | S.D. | t-test value | Mean Difference | P-value |
|---|---|---|---|---|---|---|
| Baseline | Allopurinol | 82.80 | 7.37 | 0.194 | 0.400 | 0.847 |
| | Febuxostat | 82.40 | 7.23 | | | |
| At 4 months | Allopurinol | 58.80 | 7.81 | 1.510 | 2.800 | 0.138 |
| | Febuxostat | 56.00 | 5.00 | | | |
| At 8 months | Allopurinol | 50.40 | 14.57 | 2.140 | 9.600 | 0.038* |
| | Febuxostat | 40.80 | 17.06 | | | |
| At 12 months | Allopurinol | 30.00 | 10.41 | 3.578 | 8.000 | 0.001* |
| | Febuxostat | 22.00 | 4.08 | | | |




**SAD (subjects assessment of disease activity)**

**SAD (subject's assessment of *disease activity*)** was taken at baseline and after every 4 months interval for 12 months. No statistical significant difference was observed at the baseline score. But there was statistical significant difference when inter group comparison was done between the two groups at the end of 4 months till the end of 12 months.

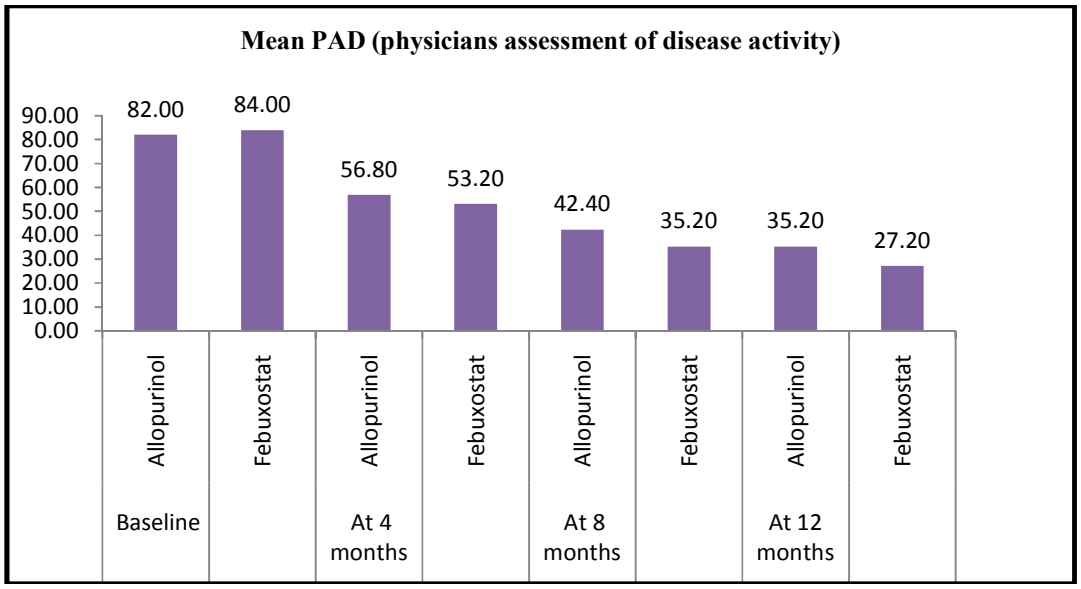
| SAD (subjects assessment of disease activity) | Drug group | Mean | S.D. | t-test value | Mean Difference | P-value |
|---|---|---|---|---|---|---|
| Baseline | Allopurinol | 84.00 | 5.00 | 1.608 | 2.400 | 0.114 |
| | Febuxostat | 81.60 | 5.54 | | | |
| At 4 months | Allopurinol | 60.80 | 10.38 | 2.575 | 6.800 | 0.013* |
| | Febuxostat | 54.00 | 8.17 | | | |
| At 8 months | Allopurinol | 46.80 | 8.02 | 3.176 | 8.000 | 0.003* |
| | Febuxostat | 38.80 | 9.71 | | | |
| At 12 months | Allopurinol | 35.20 | 10.85 | 2.736 | 8.000 | 0.009* |
| | Febuxostat | 27.20 | 9.80 | | | |




**PAD (physician's assessment of disease activity)**

**PAD (physician's assessment of disease activity)** was taken at baseline and after every 4 months interval for 12 months. No statistical significant difference was observed at the baseline score as well as after the end of 4 months. But there was statistical significant difference when inter group comparison was done between the two groups at the end of 8 months till the end of 12 months.

| PAD (physicians assessment of disease activity) | Drug group | Mean | S.D. | t-test value | Mean Difference | P-value |
|---|---|---|---|---|---|---|
| Baseline | Allopurinol | 82.00 | 7.64 | -0.894 | -2.000 | 0.376 |
| | Febuxostat | 84.00 | 8.17 | | | |
| At 4 months | Allopurinol | 56.80 | 14.35 | 1.130 | 3.600 | 0.264 |
| | Febuxostat | 53.20 | 6.90 | | | |
| At 8 months | Allopurinol | 42.40 | 8.31 | 3.286 | 7.200 | 0.002* |
| | Febuxostat | 35.20 | 7.14 | | | |
| At 12 months | Allopurinol | 35.20 | 12.95 | 2.545 | 8.000 | 0.014* |
| | Febuxostat | 27.20 | 8.91 | | | |



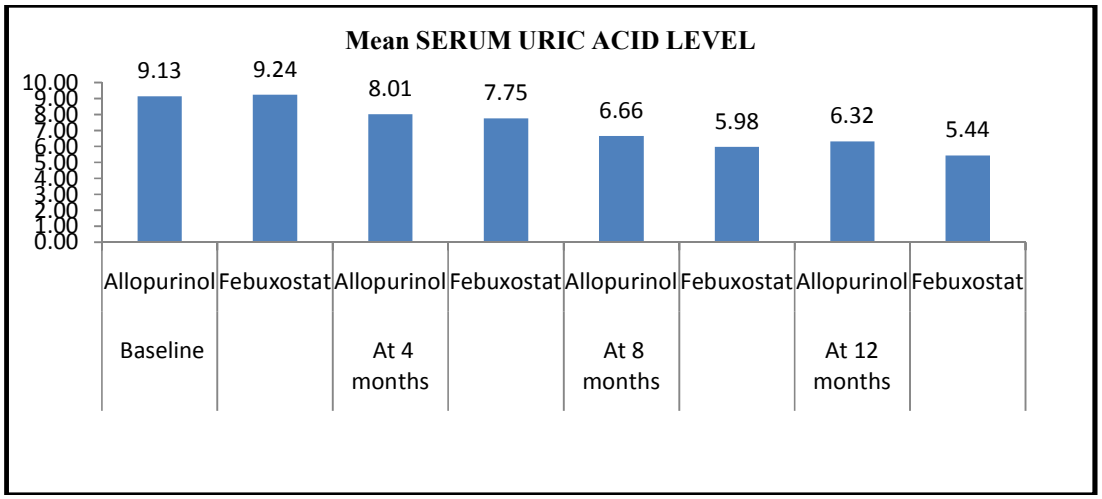

**SECONDARY END POINTS**

**SERUM URIC ACID LEVEL**

**SERUM URIC ACID LEVEL** was taken at baseline and after every 4 months interval for 12 months. No statistical significant difference was observed at the baseline score as well as after the end of 4 months. But there was statistical significant difference when inter group comparison was done between the two groups at the end of 8 months till the end of 12 months.

| SERUM URIC ACID LEVEL | Drug group | Mean | S.D. | t-test value | Mean Difference | P-value |
|---|---|---|---|---|---|---|
| Baseline | Allopurinol | 9.13 | 0.45 | -0.697 | -0.109 | 0.489 |
| | Febuxostat | 9.24 | 0.64 | | | |

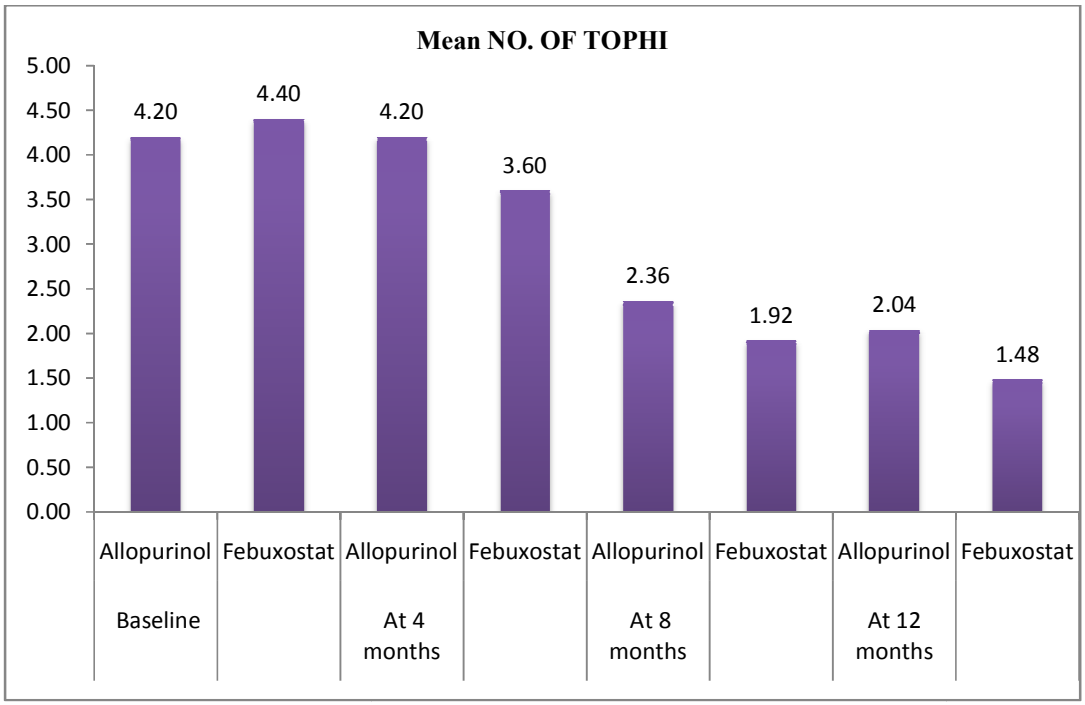
| | | | | | | |
|---|---|---|---|---|---|---|
| At 4 months | Allopurinol | 8.01 | 0.89 | 1.207 | 0.261 | 0.233 |
| | Febuxostat | 7.75 | 0.62 | | | |
| At 8 months | Allopurinol | 6.66 | 1.27 | 2.402 | 0.681 | 0.020* |
| | Febuxostat | 5.98 | 0.63 | | | |
| At 12 months | Allopurinol | 6.32 | 1.42 | 2.871 | 0.882 | 0.006* |
| | Febuxostat | 5.44 | 0.59 | | | |




**NUMBER OF TOPHI**

**NUMBER OF TOPHI** was taken at baseline and after every 4 months interval for 12 months. No statistical significant difference was observed at the baseline score. But there was statistical significant difference when inter group comparison was done between the two groups at the end of 4 months and at the end of 12 months.

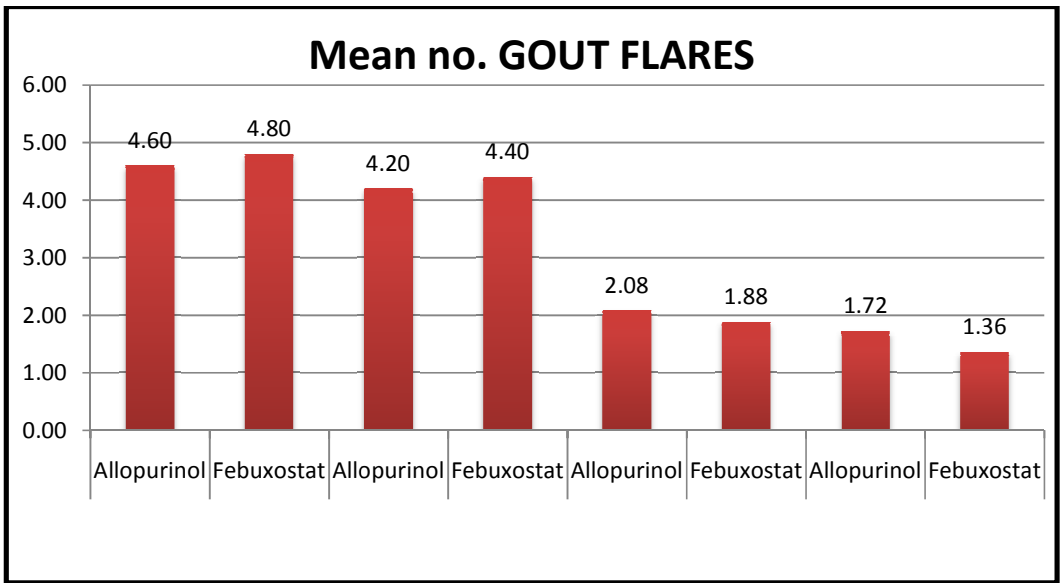
| NO. OF TOPHI | Drug group | Mean | S.D. | t-test value | Mean Difference | P-value |
|---|---|---|---|---|---|---|
| Baseline | Allopurinol | 4.20 | 0.76 | -1.095 | -0.200 | 0.279 |
| | Febuxostat | 4.40 | 0.50 | | | |
| At 4 months | Allopurinol | 4.20 | 0.76 | 3.286 | 0.600 | 0.002* |
| | Febuxostat | 3.60 | 0.50 | | | |
| At 8 months | Allopurinol | 2.36 | 0.95 | 1.917 | 0.440 | 0.061 |
| | Febuxostat | 1.92 | 0.64 | | | |
| At 12 months | Allopurinol | 2.04 | 0.79 | 2.979 | 0.560 | 0.005* |
| | Febuxostat | 1.48 | 0.51 | | | |




**GOUT FLARES**

**GOUT FLARES** was taken at baseline and after every 4 months interval for 12 months. No statistical significant difference was observed at the baseline score till the end of 8 months. But there was statistical significant difference when inter group comparison was done between the two groups at the end of 12 months.

| GOUT FLARES | Drug group | Mean | S.D. | t-test value | Mean Difference | P-value |
|---|---|---|---|---|---|---|
| Baseline | Allopurinol | 4.60 | 0.50 | -1.549 | -0.200 | 0.128 |
| | Febuxostat | 4.80 | 0.41 | | | |
| At 4 months | Allopurinol | 4.20 | 0.41 | -1.549 | -0.200 | 0.128 |
| | Febuxostat | 4.40 | 0.50 | | | |
| At 8 months | Allopurinol | 2.08 | 0.57 | 1.207 | 0.200 | 0.233 |
| | Febuxostat | 1.88 | 0.60 | | | |
| At 12 months | Allopurinol | 1.72 | 0.46 | 2.292 | 0.360 | 0.026* |
| | Febuxostat | 1.36 | 0.64 | | | |




**SAFETY END-POINTS**

No serious adverse events were reported by the subjects during the study period.

**DISCUSSION**

The study was designed to confirm the effects of the two most commonly used urate lowering drugs (Allopurinol &Febuxostat) in patients of gout. **Firstly**, we wanted to assess out of two drugs which one is more efficacious and giving early onset of symptomatic pain relief. **Secondly**, which one is more efficacious in terms of lowering the serum uric acid level, reducing the gout flares and no. of tophi.

A study from Vellore revealed that 15.8% of the affected patients are less than 30 years of age; urban Indian population is involved more than the rural population and due to increased prevalence of metabolic syndrome in younger population, the first attack of gout occurs a decade earlier to them.[7]Another Indian study showed that high uric acid level is associated with laboratory and anthropometric parameters of metabolic syndrome.[8]

The **mean age** of the patients was 53.8 years, with a range of 39 to 67 years and 59.72 years, with a range of 37 to 81 years in the allopurinol and febuxostat group respectively. The incidence of gout increases rapidly between the ages of 30 and 50 years, and the prevalence then continues to increase with age.

Literature states that the prevalence of gout is generally higher in men than in women, although this is reversed after women reach menopause, whereupon women are more afflicted by gout than men[3], principally because oestrogen promotes urate wasting in the urine. In present study, most of the women enrolled in the study were postmenopausal.

It is well known that various food stuffs are associated with acute gout attacks.[5]The following triggers of acute gout attacks were listed by patients at the baseline: red meat, alcoholic, beverages, tomatoes, carbonated beverages, fruit, green vegetables, white bread, sweets, nuts, porridge and fried eggs.

In present study, based on the **dietary intake** of the subjects, 25% were classified as red meat, 24% as alcoholic beverages, 15% as tomatoes, 13% as carbonated beverages, 8% as fruit, 4% as green vegetables, 3% as white bread and 9% as other food stuff.This clearly indicates the importance of red meat and alcoholic beverages as potential triggers for acute gout flares. Many of the patients at their follow up stated that they tried to decrease their intake of the above mentioned foodstuffs in order to avoid acute gout attacks.Increased seafood intake has long been referred to as a risk factor for gouty flares.[5]Contrary to this, only one or two patients listed any form of seafood as a potential trigger.

The primary efficacy criterion in our study was the change in **100mm VAS scale** after the patient was asked to take a 20m walk. Patients were asked to complete visual analogue scales at their every visit; namely subject's assessment of pain (**SAP**) and subject's assessment of disease activity (**SAD**). Physicians were asked to complete a physician's assessment of disease activity (**PAD**) for each patient.

All of the visual analogue scales (SAP, SAD and PAD) showed a decrease at every interval i.e. from baseline to the final follow up. In **SAP**, both drugs are efficacious in reducing the pain. But febuxostat gave early symptomatic pain relief and had longer duration of action in comparison to allopurinol as statistically significant difference is seen at the end of $8^{th}$and $12^{th}$month. In **SAD,** the significant difference was observed at the end of $4^{th}$ month and remained significant till the end of $12^{th}$ months. In **PAD,** the statistically significant difference is seen at the end of $8^{th}$ and $12^{th}$ month.

When comparing the baseline mean subjects assessment of disease activity score to that of the baseline mean physician's assessment of disease activity score, it can be seen that patients mean score was higher than that of the physician's mean score.

This could possibly indicate that patients tend to overestimate their disease activity in periods where they do not experience gout attacks. This leads us to question whether the subject's assessment of pain was also overestimated. But unfortunately this question cannot be answered, as only the patients, not the physician, completed an assessment of pain.

Upon comparison of the follow up visit's mean assessments of disease activity, it was found that mean SAD score was high than mean PAD score at the $4^{th}$ and $8^{th}$ month interval. At the $12^{th}$ month, it was found that both the mean SAD and PAD scores were similar to each other, indicating that while each individual patient's assessment of disease activity may not have agreed with that of the physician, the general trend in mean scores shows similarity.

So, while scores shows that patients tend to overestimate the severity of their gout attacks, their scores generally remain in the same range as the physician's scores, which show that although the patient's assessment of pain and disease activity is subjective, it is still a reliable indicator of gout activity.

Visual analogue scales are frequently used to assess gout in clinical trials. As such the validity of the scale needs to be established. One research team assessed the validity of pain and patient global scales in chronic gout patients involved in the pegloticase clinical trials. They discovered that visual analogue scales correlated with results obtained from tender and swollen joint counts as well as the SF-36, a body pain subscale. The authors concluded that the visual analogue scales are valid outcome measures for the evaluation of gout patients.[12]Another study, Taylor TH et.al[13], also used VAS for measuring pain in primary joints for 10 days. Mean daily VAS pain scores did not differ significantly between study groups at any point between days 1 and 10.

The secondary efficacy end point was the percentage reduction from baseline sUA at each study visit and maintained sUA<6.0 mg/dl. Among all subjects, mean % sUA reductions from baseline ranged from 7 to 18% and 9 to 26% across all visits for allopurinol and febuxostat respectively. Allopurinol and febuxostat both decreased the serum uric acid level but febuxostat was more effective than allopurinol. At each visit, the sUA decreased but statistically significant difference was seen at $8^{th}$ month and at $12^{th}$ month and maintained their sUA level < 6.0 mg/dl. Schumacher HR et al showed that mean % sUA reductions from baseline ranged from 45 to 59% across all visits. Across doses % reductions in sUA were similar at final visit, with % reductions from baseline of 49.2, 47.1, and 50.7% for febuxostat doses of 40, 80 and 120 mg respectively.Maintenance of sUA in this range has resulted in clinical benefits of tophus resolution and decreased gout flare incidence over the long term.[14]Another study also showed that febuxostat, at a daily dose of 80mg or 120mg, was more effective than allopurinol at the commonly used fixed daily dose of 300mg in lowering serum urate. [11]

Becker MA et al showed that febuxostat was more effective than allopurinol in terms of reductions of gout flares and no. of tophi.[11]Present study also showed that febuxostat was more effective in reducing the no. of tophi. At the end of the $4^{th}$ month and $12^{th}$month statistically significant difference was seen, at the end of the $8^{th}$ month no. of tophi decreases but no statistical difference was observed. Gout flares diminished at the end of the $12^{th}$ month.Schumacher HR et al showed that the percentage of subjects that required treatment for gout flares declined to zero during the $5^{th}$ year of treatment.

Jackson RL et al showed that febuxostat 80mg was significantly more efficacious than febuxostat 40 mg or allopurinol in achieving the sUA< 6.0mg/dl in gout patient's ≥ 65 years of age. Febuxostat 40 mg was also superior to allopurinol in this population. In subjects with mild to moderate renal impairment, significantly greater ULT efficacy was observed with febuxostat 40mg and 80mg. Flare rates declined steadily in all treatment groups.[15]Becker MA et al also proved that urate lowering efficacy of febuxostat 80 mg exceeded that of febuxostat 40 mg and allopurinol(300/200mg). In subjects with mild/moderate renal impairment, both febuxostat doses were more efficacious than allopurinol and equally safe.[16]

Both the urate lowering drugs (Allopurinol and Febuxostat) reduces the sUA level and provides the symptomatic pain relief in the patients with hyperuricemia and gout. Both drugs improve the functionality of the joints and improve the quality of life of the patients with gout. Long term maintenance of both the drugs provides the reduction in the gout flare and no. of tophi. Both drugs are well tolerated and quite safe.

## CONCLUSION

From this study it was concluded that Visual analogue scales proved to be a valid measure of gout activity. It was found that patients tend to slightly overestimate their level of disease activity when comparing patient responses to those of physician. VAS pain, SF-36 pain and patient global VAS are valid outcome measures in patients with chronic gout. Febuxostat and allopurinol provided symptomatic and functional relief in the patients with gout. However, in the view of statistical data, we consider that febuxostat may be first choice if early considerable symptomatic improvement is required.Both allopurinol and febuxostat are effective in the treatment of chronic hyperuricemia. Febuxostat has some advantages over allopurinol, being a non-purine xanthine oxidase inhibitor with lesser side effects and drug interaction. Long term use of these drugs reduces the gout flare, tophi and maintains the sUA< 6.0mg/dl.

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