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Research Article

A Comparative Study of Safety and Efficacy of Allopurinol and Febuxostat in Patients with Hyperuricemia

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Abstract

Objective: To Evaluate the comparative study of safety and Efficacy of Allopurinol and Febuxostat in patients with hyperuricemia. To report adverse effects of allopurinol and febuxostat. Evaluation of Laboratory investigations by Serum Uric Acid Test.

Introduction: Hyperuricemia is defined by a rise in serum urate levels > 7.0mg/Dl. It is caused by a combination of a factors including nutrition, genetic predisposition and urate overproduction or underproduction. Uric acid is a by-product of protein metabolism. Allopurinol and Febuxostat is used to treat hyperuricemia patients (chronic gout) with a dose of 100-300 mg and 40-80 mg respectively.

Methodology: Out of 200 patients with hyperuricemia were randomly assigned to allopurinol group (100) and febuxostat group (100) in that both males and females are equally randomized. The Duration of the study is 6 months and was designed as a prospective, comparative, observational and follow-up component. This study was carried out in patients suffering from hyperuricemia to evaluate the comparative study of safety and efficacy of Allopurinol and Febuxostat in the Department of Orthopaedics, Durgabai Deshmukh Hospital, 300 bedded multi-speciality hospital from January 2021. All statistical analysis are performed by using IBM SPSS windows V24. Descriptive statistics like mean, SD, are calculated for Age, height, weight, BMI, serum uric acid. ANCOVA was performed to compare mean values of uric acid. X2- test were used to study the association between the BMI category and drugs.

Results: We found no statistically significant correlation between age, height, weight, or BMI and drugs in our study. Using the x2-test, we found no correlation between BMI category and drug in our study. In both groups, when gender is considered, there is a statistically significant difference between age and drugs for female patients, but not for male patients. Out of 200 patients in our study, 116 patients (61 men and 55 women) had adverse effects that were reported, and 84 patients (39 men and 45 women) had no adverse effects. Compared to other drugs allopurinol has more side effects.

Conclusion: In our study, it is proved that febuxostat with a dose 40-80mg/day is shown to be be more efficacious and safer in reducing serum urate concentration than allopurinol 100-300mg/day. Allopurinol shows a major adverse effect as compared to febuxostat.

Keywords: Hyperuricemia; Uric Acid; Protein Metabolism; Xanthine Oxidase

Introduction

Hyperuricemia is defined by a increase in serum urate levels, which is the sole observable abnormality. It is a condition in which uric acid serum levels are higher above the usual urate threshold level of 8.0 mg/dL in males and 7.0 mg/dL in women [1]. The solubility parameters such as pH, temperature, of mono sodium crystals are present. The eradication of acute gout attacks and the mobilisation of urate crystals from soft tissue are the general aim for decreasing uric acid blood concentrations.[2] In around 90% of instances, renal under excretory of urate is the major cause of hyperuricemia, while overproduction is the reason in fewer than 10% [3].

Allopurinol is the most widely prescribed medication for hyperuricemia in doses of 100 to 300 mg per day, with a maximum recommended dose of 800 mg per day [4]. The daily dose is 300mg on average and renal insufficiency patients may encounter severe or life-threatening side effects [5]. Adverse effects of this drug includes Dermatological, GI effects, Rarely stevens Johnson syndrome or toxic epidermal necrolysis which can be fatal and Neurological disorders [6]. Febuxostat, a powerful xanthine oxidase inhibitor, has minimal effect on other purines along pyrimidine metabolic enzymes pathways and is largely metabolized in the liver through glucuronide production and oxidation processes. Febuxostat is used to treat hyperuricemia patients with a dosage of 80 and 120 milligrams. respectively [5]. Febuxostat (FEB) which has a greater extent lipid solubility than allopurinol, a different carboxyl group, and is removed by the bile. As a result, febuxostat is regarded to be safe for usage in kidney disease patients [7]. The adverse effects of this drug include Diarrhoea, Headache, nausea, Joint pain and Rash [8]. In individuals who are taking mercaptopurine, azathioprine, or theophylline, febuxostat is not indicated [9].

In individuals with hyperuricemia and gout, febuxostat, is show greater efficient than the drug allopurinol in decreasing Urate levels [10]. Patients receiving febuxostat experienced immediate and significant drops in their serum uric acid levels during these clinical trials. The average uric acid level in blood in females is between 1.5 and up to 6 mg/dl, but in men is between 2.5 and upto 7mg/dl. Uric acid crystals develops when uric acid levels are reached higher than normal stage they develops into monosodium urate(msu) [11]. According to statistics, it is defined by serum urate levels two standard deviations above the population mean [12].

Uric acid is a by-product of protein metabolism. Hypoxanthine, a breakdown product of purine nucleotides and cellular nucleoproteins, is converted to xanthine and xanthine to uric acid by the enzyme xanthine oxidase [4]. The breakdown of cellular nucleoproteins, de novo generated purine nucleotides, and dietary purine consumption all contribute to plasma urate. The enzymes HGPRT (Hypoxanthine and Guanine Phosphoribosyl Transferase), Adenine phosphoribosyl transferase (APRT) recycle a portion of purine bases produced during cellular breakdown (APRT) [6].

The significance of conducting this study to compare the safety and efficacy of both allopurinol and febuxostat in hyperuricemia patients in order to achieve a decrease in serum uric acid levels to normal levels.

Materials and Methods

For this study, consent of Institutional Ethics Committee was carried out at the Durgabai Deshmukh Hospital and Research Centre (AMS), Vidyanagar, Hyderabad in the Department of General Medicine and Orthopaedics. This prospective, comparative, observational and follow up conducted for 6months in department of General Medicine and Orthopaedics, Durgabai Deshmukh Hospital and Research Centre (AMS) a 300 bedded Multi-speciality Hospital.

We conducted a comparative study on the safety and effectiveness of allopurinol and febuxostat in hyperuricemia patients in which SU > 7.0mg/dL. Out of 200 patients with hyperuricemia were randomly assigned to allopurinol group (100) and febuxostat group (100) in that both males and females are equally randomized.

Age	Allopurinol		Febuxostat		Total
	Males	Females	Males	Females	
16-25	7	3	2	3	15
26-35	15	9	12	8	44
36-45	8	10	13	10	41
46-55	5	9	6	12	32
56-65	5	5	10	6	26
66-75	8	9	3	9	29
76-85	2	5	4	2	13
	T = 50	T = 50	T = 50	T = 50	T = 200

Table 1: Age distribution in two patient groups with hyperuricemia.

BMI	No. of patients	Percentage
Underweight	1	0.5
Ideal weight	44	22
Overweight	153	76.5
Obese	2	1

Table 2: Body mass index in hyperuricemic patients.

Statistical analysis

All statistical Analysis calculated by Using IBM SPSS (Statistical Package for the Social Sciences) windows version 24 was used for all statistical analysis. Age, height, weight, BMI, UA, and proportion for gender and BMI categories were computed using descriptive statistics such as mean and SD. The T-test was performed to compare mean values across medicines at different time points. Increments were also calculated and compared across drugs using T-test. ANCOVA (Analysis of Co-Variance) was performed to compare mean values of Uric Acid (UA) adjusting the baseline values. X2- test were used to study the association between the BMI category and drugs. Level of significance was considered as 0.05 value.

Criteria for inclusion

- Patients with a uric acid level of more than 7.0 mg/dL who aren't taking any uric acid-lowering medicines and are suspected of having Gout.
- Patients with gouty arthritis who have had it in the last six months.
- Adult male and female patients who were 20 years or older at the time of informed consent acquisition.
- Patients who have not been admitted to a medical facility (out-patient status).
- Patients who consent to participate in the study in writing.

Criteria for exclusion

- Patients with a history of hypersensitivity to febuxostat, colchicine, or NSAIDs, or those who have never been exposed to them.
- Patients who have used any uric acid-lowering medication in the last four weeks.
- Patients who have or have had a malignant tumour as a complication that required treatment in the past.
- Patients using mercaptopurine hydrate or azathioprine as a treatment.
- Peptic ulcer patients with a significant hematological condition.
- Patients with a significant heart condition.
- **Data collection:** The patient case sheet will be used to collect all relevant and necessary information.
- **Dose: Allopurinol dose:** 100-300 mg/daily, Febuxostat dose: 40-80mg OD
- **Method of study:** Patients with hyperuricemia who visited the OPD and were admitted to the Durgabai Deshmukh Hospital will be assessed in a study. Baseline demographic data will be collected from the patient case record. The subjects are separated into two groups based on the induction medication they received.
- **Group-A:** Allopurinol-treated subjects and Group-B: Febuxostat-treated subjects. Allopurinol and Febuxostat, which are both administered to patients with hyperuricemia, have been studied for their safety and efficacy. The obtained results are analyzed using IBM SPSS software (Statistical Package for the Social Sciences) version 24 for Windows.

Results and Discussion

In our study we concluded that their no statistical significant between Age, Height, weight, BMI by Drug. When compared to gender in both groups there is a statistical significant between Age and Drug in female patients and in male patients there is no statistical significant. In both groups of males and females of serum uric acid at day 1 and day 15 had concluded that there is a statistical significant between serum uric acid and drug. By using X^2 - test it was concluded that there Is no association between BMI categories and drug. The mean value of febuxostat- 8.4 was found to be significantly higher than allopurinol mean-7.8 at day 1 UA. At day 15 same result had observed with treatment. The drug Increment of febuxostat with a mean value of 3.3 was significantly higher than allopurinol (1.31) mean value. Hence it is statistically significant between serum uric acid and Drug by this Febuxostat shows greater efficacy than allopurinol.

In our study, out of 200 patients undergoing allopurinol and febuxostat therapy, 116 patients (61 men and 55 women) were reported to have adverse effects, and 84 patients (39 men and 45

women) were found to have no adverse effects. From this study we reported that major adverse effects are Erythematous rash, Renal failure, Joint Pain and minor adverse effects are eosinophilia, cutaneous vasculitis, Nausea Headache, Diarrhoea this adverse effects are all related to drug allopurinol on other hand the drug Febuxostat were reported with major AE like liver failure and minor AE like Arthralgia, hypersensitivity, Erythematous rash, skin rash with eruption and eczema. Most adverse effects are occurred due to drug allopurinol as compared to febuxostat.

Efficacy parameters

Variable	Allopurinol Mean ± Standard Deviation	Febuxostat Mean ± Standard Deviation	T-Value	P-Value
Day 1(UA)	7.77 ± 0.82 SD	8.39 ± 0.94 SD	4.942	0.000
Day 15(UA)	6.46 ± 0.74 SD	5.08 ± 1.28 SD	9.290	0.000
Drug Increment	1.31 ± 0.54 SD	3.31 ± 0.92 9SD	18.57	0.000

Table 3: Mean ± standard deviation values of serum uric acid by drug for each group by using t-test.

- DAY 1[UA]- Initially the mean value of febuxostat 8.39 was found to be significantly higher than Allopurinol mean value 7.77 during at Day 1 (UA) treatment.
- DAY 15 [UA] - Same trend was observed as Day 1 with the treatments.
- The Drug increment of Febuxostat with a mean value of 3.3 was significantly higher than Allopurinol of mean value 1.31.*
- From our study it is concluded that the p-value [0.000] was < critical p-value [0.05] hence, it is statistically significant between serum uric acid and drug.

Variable	Allopurinol Mean ± Standard Deviation	Febuxostat Mean ± Standard Deviation	T-Value	P-Value
Age	51.26 ± 18.00 SD	47.24 ± 17.54 SD	1.6	0.111
Height	171.78± 9.20 SD	170.77 ± 9.05 SD	0.782	0.435
Weight	70.39± 9.42 SD	70.10 ± 8.01 SD	0.234	0.815
BMI	23.76 ±1.74 SD	23. 98 ± 1.32 SD	1.000	0.319

Table 4: Mean ± standard deviation values of age, height, weight, BMI, by drugs for each group by using t-test.

- From the above table data it is concluded that there is no statistical significant between Age and Drug, where calculated T-value (1.6) is < Tabulated T-value (1.96) at 5% level of significance with 198 degree of freedom, hence null hypothesis accepted.
- From the above table data it is concluded that there is no statistical significant between height and Drug, where calculated T-value (0.782) is < Tabulated T-value (1.96) at 5% level of significance with 198 degree of freedom, hence null hypothesis accepted.
- From the above table data it is concluded that there is no statistical significant between weight and Drug, where calculated T-value (0.234) is < Tabulated T-value (1.96) at 5% level of significance with 198 degree of freedom, hence null hypothesis accepted.
- From the above table data it is concluded that there is no statistical significant between BMI and Drug, where calculated T-value (1.00) is < Tabulated T-value (1.96) at 5% level of significance with 198 degree of freedom, hence null hypothesis accepted.

Independent sample test

Gender	Drugs and test	Age	Day 1(UA)	Day15(UA)
Male	ALLOPURINOL Mean ± Standard Deviation	45.22 ± 16.82SD	7.79 ± 0.76 SD	6.55 ± 0.65 SD
	FEBUXOSTAT Mean ± Standard Deviation	45.92 ± 16.82 SD	8.51 ± 0.92 SD	5.37 ± 1.20 SD
	T-Value	0.194	4.273	6.117
	P-Value	0.847	0.000	0.000
Female	Allopurinol Mean ± Standard Deviation	57.30± 17.23SD	7.76 ± 0.89 SD	6.55 ± 0.65 SD
	Febuxostat Mean ± Standard Deviation	48.56± 15.81SD	8.28 ± 0.96 SD	4.79 ± 1.31 SD
	T-Value	2.642	2.788	7.197
	P-Value	0.010	0.006	0.000

Table 5: Gender: Male and Female Groups Statistics by Using T-Test.

- **Age:** Results form our study states that calculated T-value for males is (0.194) < tabulated T-value (1.96) and in females calculated T-value (2.642) is > tabulated T-value (1.96) at 5% level of significance with 98 d.f. Hence it is concluded that there is no statistical significant between Age and Drug in male patients and in females patients there is statistical significant between Age and Drugs.
- **Day 1 (UA):** Data of our study states that calculated T-value in males is (4.273) > tabulated T-value (1.96) and in females calculated T-value is (2.788) > tabulated T-value (1.96) at 5% level of significance with 98 d.f, hence it is concluded that there is statistical significant between serum uric acid and Drug in both male and female patient with hyperuricemia. Where null hypothesis is rejected.
- **Day 15 (UA):** Data of our study states that calculated T-value (6.117) is > tabulated T-value (1.96) and in females calculated T-value (7.197) is > tabulated T-value (1.96) at 5% level of significance with 98 d.F, hence it is concluded that there is highly statistical significant between serum uric acid and Drug in both males and female patient with hyperuricemia. Null hypothesis is rejected.

BMI	Allopurinol No. of patients	Febuxostat No of patients	Total No of Patients	X^2 value	P-value
Underweight	1	0	1	1.150	0.76
Ideal Weight	23	21	44		
Overweight	75	78	153		
Obese	1	1	2		

Table 6: Chi-square test between BMI categories and drugs.

In our study it is known that there is No Association between BMI Categories and Drugs by using x2 (chi-square) test. where calculated X^2 value (1.150) is lesser than tabulated X^2 value (7.81) says that there is no significance difference between BMI and drug at 5% level of significance, Hence null hypothesis is accepted.

Safety parameters

Treatment group	ADRs Present	ADRs Absent
Allopurinol	71	29
Febuxostat	45	55

Table 7: Depiction of adverse effects in treatment groups.

- Out of 100 patients in allopurinol group, 71 patients are with adverse effects and 29 patients are without adverse effects.
- Out of 100 patients in Febuxostat group, 45 patients are with adverse effects and 55 patients are without adverse effects.

Adverse effects	Allopurinol		Febuxostat	
	Male	Female	Male	Female
ADRs Present	34	37	27	18
ADRs Absent	16	13	23	32

Table 8: Distribution of adverse effects based on gender.

- In our study, out of 100 patients of allopurinol group, 34 male and 37 female patients are reported with adverse effects and 16 Male, and 13 Female patients are without Adverse effects.
- In our study, out of 100 patients of Febuxostat group, 27 male and 18 female patients are reported with adverse effects and 23 Male and 32Female patients are without Adverse effects.

Adverse effects	No. of Patients		Total No of Patients
	Males	Females	
Erythematous Rash	6	2	8
Hypersensitivity	3	2	5
Joint pain	5	4	9
Liver failure	2	3	5
Renal failure	3	6	9
diarrhoea	2	2	4
Headache, Dizziness	1	2	3
Eosinophilia	1	2	3
Cardiac disorders	1	5	6
Peripheral Neuritis	3	2	5
Cutaneous vasculitis	1	2	3
Nausea, Vomiting	2	2	4
Skin Rash (eruption, eczema)	4	3	7

Table 9: Distribution of adverse effects in allopurinol group.

- Out of 100 patients of allopurinol group in males we identified Major ADRs are Erythematous Rash, joint Pain and in females Renal failure, cardiac disorders.

Adverse effects	No of patients		Total No of Patients
	Males	Females	
Arthralgia	1	1	2
Liver failure	7	3	10
Renal failure	2	1	3
Erythematous Rash	1	1	2
diarrhoea	1	2	3
Headache, Dizziness	2	3	5
Eosinophilia	3	1`	4
Cardiac disorders	2	2	4
Nausea, Vomiting	2	1	3
Skin Rash (eruption, eczema)	1	1	2
Joint Pain	3	2	5
Hypersensitivity	2	0	2

Table 10: Distribution of adverse effects in febuxostat group.

- Out of 100 patients in febuxostat group both males and females we identified Major ADRs are liver failure and in females Headache, dizziness are additional major ADRs.

Conclusion

we have conducted a study of comparing the safety and efficacy of allopurinol and febuxostat in patients of hyperuricemia. From the above data it is proved that febuxostat with a dose 40-80mg/day is shown to be more efficacious and safe in reducing serum urate concentration than allopurinol 100-300mg/day.

Ethics and Consent

Permission was obtained from the ethics committee. The entire study was conducted according to the AHA/ASA guidelines Upon receiving the informed consent form, all patients who meet the study criteria were included in the study. All the relevant and necessary data was collected from patient case reports, laboratory reports, prescriptions and by interviewing the patients.

Conflicts of Interest

None.

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