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Original Article

Comparison of Efficacy of Febuxostat with Allopurinol in Lowering Serum Urate Levels

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Abstract

Background: To compare the efficacy of Febuxostat with Allopurinol in lowering serum urate levels

Methods: In this randomized controlled trial a total of 60 patients with hyperuricemia above 18 years of age were included. Thirty patients were given Allopurinol and 30 patients were given Febuxostat for 4 weeks. Hyperuricemia was defined as serum uric acid level of greater than 6mmol/L. Uric acid was measured at 2 and 4 weeks from start of treatment. Chi-square test was applied to compare the efficacy of drugs among the two groups.

Results: After 4 weeks of therapy uric acid reduced to <6mg/dl successfully in 42/60 patients (70 %) . In Febuxostat group 26/30 (86.7%) patients responded to treatment with uric acid levels <6mg/dl while in Allopurinol group 16/30 (53.3%) patients showed uric acid <6mg/dl with a significant p= 0.005 . Febuxostat was effective in 22/25 (88%) of male (mean age 57.50 ± 8.695years) and 4/5(80%) of female(mean age 57.75 ± 8.578 years)patients while Allopurinol was effective in 12/23 (52.2%) of males (mean age 56.33 ± 11.758 years) and 4/7 (57.1%) of females (mean age 54.25 ± 8.770 years) .

Conclusion: The efficacy of treatment was significantly higher in Febuxostat group as compared to the Allopurinol group.

Key words: Febuxostat, Allopurinol , Hyperuricemia

Introduction

Owing to a multitude of factors hyperurecemia affects a significant proportion of people. It results in the accumulation of urate crystals in joints and tissues leading to gout which is an independent risk factor for cardiovascular disease and metabolic syndromes.Uric acid is the end product of protein metabolism in the human body. Increased levels of uric acid in the serum are the result of either increased production or decreased excretion by the kidneys. [1] They may also be increased due to certain metabolic disorders and drugs such as thiazide diuretics, low dose asprin and pyrazinamide .[2]

Increased levels of uric acid result in crystallization of uric acid in joints and tissues leading to gout; an acute arthritis where there is severe pain secondary due to inflammation of joints mostly the big toe. Aspiration of joint fluid reveals needle shaped crystals, negatively birefringent under polarized light. Furthermore uric acid can also deposit in tissues as monosodium urate monohydrate crystals known as tophi, specially around pinna of ear , tendons and bones . Gout can also present as renal stones. [3] -Incidence of hyperuricemia and gout is increasing mostly due to dietary habits and sedentary life style of current generation.[4]

The drugs available to lower uric acid levels fall broadly into 3 categories; uric acid production inhibitor eg allopurinol and febuxostat , uric acid excretors (uricosouric agents) eg probenecid and uric acid metabolizer eg uricase. Uric acid production inhibitors act by inhibiting xanthine oxidase and are first line drugs for hyperuricemia.[5]

In one study target uric acid level (6mg/dl) was achieved in 82% of patients in febuxostat group as compared to 47.3% in allopurinol group. [4] European and Japanese guidelines of management for gout recommend that serum urate concentration should be maintained below 6.0 mg/dL to promote crystal dissolution leading to prevention of recurrent gouty attack. [6] Uricosuric agents are considered as second line treatment while uricase is an expensive drug reserved only for resistant hyperuricemia. [7]Urate lowering therapy may be indicated in patients with hyperuricemia who are suffering from hypertension, diabetes mellitus, ischemic heart disease and renal insufficiency. [8]

Patients and Methods

This was a randomized controlled study done at Department of Medicine Unit 1, Benazir Bhutto Hospital Rawalpindi for duration of six months ,i.e., June 2015 to December 2015. Total sample size was 60. Patients were divided in two groups with 30 patients in each group. Sampling technique used was Consecutive (Nonprobability) sampling. Patients with age 18 to 75 years,patients not treated for hyperuricemia in past, patients with hyperuricemia (>6mg/dl) were included in the study.Patients having suspicion of malignancy and asymptomatic patients other than hypertension, diabetes mellitus, ischemic heart disease and renal insufficiency were excluded from the study.Permission was taken from hospital ethical committee before the start of study. An informed written consent was taken from all the participants of study, after informing the aim of study. Patients fulfilling the inclusion criteria were instructed to take study medication in the morning,with a glass of water. Single blind method was used to preserve blinding. Randomization was done by lottery method, to allocate patients to either group A (Febuxostat group) or group B (Allopurinol group) for up to 4 weeks. Group A was given 80mg febuxostat once a day and Group B was given 100mg allopurinol three times a day (Figure 1)Serum uric acid was tested at first follow up at 2 weeks interval. If hyperuricemia did not settle at two weeks interval, an additional two weeks supply of medication was dispensed and patient was scheduled to return at week 4 for the final evaluation where serum uric acid was tested again . .Chi Square test was used to compare the efficacy in both groups. A p-value of less than 0.05 was considered statistically significant.

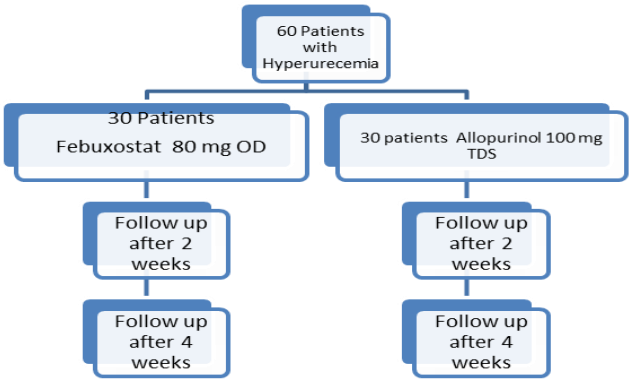

Figure 1: Framework of the Study

Results

The age of patients ranged from 32 to 74 years with a mean age of 57.60 ± 8.99 years. In the study group 48 (80 %) patients were males and 12 (20 %) patients were females. In the Febuxostat group 25/30 (83.3 %) patients were males and 5/30 (16.7 %) patients were females. In the Allopurinol group 23/30 (76.7%) patients were males and 7/30 (23.3%) patients were females.

This difference was not statistically significant; p= 0.519.The mean age of the patients in the Febuxostat group was 58.20 ± 8.467 years and the mean age of the patients in the Allopurinol group was 57.00 ± 9.599

Table 1: Summary table of all findings

Characteristics	Intervention groups							
	Group A "Febuxostat				Group B Allupurinol			
Age	N	Mean	SD	SEM	N	Mean	SD	SEM
	30	58.20	8.467	1.546	30	57.00	9.599	1.753
Gender Distribution p value = 0.653	Male		Female		Male		Female	
	25		5		23		7	
	83.3%		16.7%		76.7%		23.3%	
Comparison of efficacy after 2 weeks of treatment P Value = 0.007	Uric acid <6mg/dl		Uric acid >6mg/dl		Uric acid <6mg/dl		Uric acid >6mg/dl	
	24		6		14		16	
	80.0%		20.0%		46.7%		**53.3%**	
Comparison of efficacy after 4 weeks of treatment p value = 0.005	uric acid <6mg/dl		uric acid >6mg/dl		uric acid <6mg/dl		uric acid >6mg/dl	
	26		4		16		14	
	86.7%		13.3%		53.3%		46.7%	

years. This difference was not statistically significant; p= 0.610.Hence the two groups were similar with respect to age and gender distribution (Table 1). After 2 weeks of therapy uric acid was successfully lowered in total of 38/60 patients (63. 3 %) . In Febuxostat group 24/30 (80%) patients responded to treatment with uric acid levels <6mg/dl while in Allopurinol group 14/30 (47.6%) patients showed uric acid <6mg/dl at interval of 2 weeks with a statistically significant p = 0.007 . Febuxostat was effective in 20/25 (80%) of male (mean age 57.85 ± 9.010)and 4/5(80%) of female(mean age 57.75 ± 8.578)patients while Allopurinol was effective in 11/23 (47.8%) of males (mean age 58.55 ± 9.353) and 3/7 (42.9%) of females (mean age 58.00 ± 5.568) (Table 1) . After 4 weeks of therapy we were able to reduce uric acid to <6mg/dl successfully in of 42/60 patients (70 %) . In Febuxostat group 26/30 (86.7%) patients responded to treatment with uric acid levels <6mg/dl while in Allopurinol group 16/30 (53.3%) patients showed uric acid <6mg/dl with a significant p= 0.005.Febuxostat was effective in 22/25 (88%) of male (mean age 57.50 ± 8.695)and 4/5(80%) of female(mean age 57.75 ± 8.578)patients while Allopurinol was effective in 12/23 (52.2%) of males (mean age 56.33 ± 11.758) and 4/7 (57.1%) of females (mean age 54.25 ± 8.770)

Discussion

Uric acid is the end product of the metabolism of purine compounds. Most of uric acid circulates as the urate anion.The vast majority of mammalian species have extremely low serum urate levels (about 1 mg/dL; 60 micromol) because uric acid is converted to allantoin, a highly soluble excretory product. By contrast, uric acid is the end product of purine metabolism in humans, [1]because the human homolog of the mammalian uricase gene is structurally modified to an unexpressed (pseudogene) state. Thus, normal humans have serum urate concentrations approaching the theoretical limit of solubility of urate in serum (6.8 mg/dL) and regularly excrete urine that is supersaturated with respect to uric acid. As an example, the mean serum urate concentration is about 6 mg/dL among healthy adult white men in the United States, and the prevalence of hyperuricemia in this group is estimated to be at least 5 to 8 percent. [1]

The normal adult male has a total body urate pool of approximately 1200 mg, twice that of the adult female. [10]This gender difference may be explained by an enhancement of renal urate excretion in women of childbearing age due to the effects of estrogenic compounds, which likely reduce the number of active renal urate transporters, resulting in lesser renal tubular uric acid reabsorption and thus increased urate clearance. [11,12]

Normally, all urate measured in the body pool is believed to be soluble urate. When insoluble urate crystal deposition occurs (in gout), body pool measurements underestimate the body urate pool. Under normal steady state conditions, daily turnover of about 60 percent of the urate pool is achieved by balanced production and elimination of uric acid. [13]

Primary hyperuricemia in men frequently begins at puberty, when the lower serum urate levels characteristic of children rise into the adult male range. Normal adult male values exceed those in women of reproductive age due to enhancement by estrogenic compounds of renal urate clearance in the latter , an effect that is probably mediated by inhibition of renal urate reabsorption by organic anion transporters.[14] Thus, hyperuricemia in women is usually delayed until after menopause. [15] At that point, serum urate values in normal women increase and approximate those in normal men of corresponding age. There is a lesser rise in urate levels in postmenopausal women treated with hormone replacement therapy. [16]

Although the incidence of gout increases with increasing age irrespective of gender, [17] Incidence is appreciable from age 30 in men and only after about age 50 in women. Thus, the clinical manifestations of hyperuricemia in both men and women occur, on average, about two decades later than the initial physiologic increase in serum urate concentration. [18] This observation suggests that there is a lengthy period of asymptomatic hyperuricemia preceding the occurrence of gout. [19]

Persistent hyperuricemia of any etiology leads to serious clinical consequences including gout , renal stones and nephropathy.[20]Hyperuricemia is also independent risk factor for cardiovascular diseases.[21]All effects and consequences of hyperuricemia can be reduced significantly by lowering uric acid levels.[22] Of all measures used to lower uric acid levels, instituting uric acid lowering drugs like xanthine oxidase inhibitors is the most effective method. Until recently Allopurinol was considered drug of choice till the arrival of Febuxostat .[23]

Several international trials have been done comparing these drugs for short and long term treatments . Febuxostat is found far more superior to Allopurinol in all the trials done so far. [24, 25] A meta-analysis done recently showed the risk of any adverse event was

lower in febuxostat recipients compared to allopurinol (RR = 0.94, 95% CI = 0.90–0.99, I2 = 13%). Patients receiving febuxostat were more likely to achieve a serum uric acid of <6 mg/dl than allopurinol recipients (RR = 1.56, 95% CI = 1.22–2.00, I2 = 92%). [13]

Conclusion

1. Febuxostat 80 mg daily is more effectice in lowering serum uric acid level as compared to allopurinol 300mg daily in treatment durations as low as 2weeks to 1 month.
2. Effect of diet should also be taken into account while employing uric acid lowering regimens.

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