ORIGINAL ARTICLE

To Compare the Efficacy of Febuxostat Versus Allopurinol in patients with Hyperuricemia due to Chronic Kidney Disease

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ABSTRACT

Aim: To determine the efficacy of febuxostat versus Allopurinol in reducing level of serum uric acid among patients of hyperuricemia due to chronic kidney disease.
Study design: This Randomized Control Trials study was conducted at the Nephrology department (OPD), Jinnah Postgraduate Medical Centre, Karachi. All the patients of stage 3 and 4 chronic kidney disease and uric acid level >6.8mg / dl were selected. Patients were divided in tow groups. Patients of group A underwent oral administration of febuxostat 240mg/day and patients of group B underwent allopurinol 100mg/day for 26 weeks. Patients were followed for 24 weeks and serum uric acid level was done. The efficacy was labeled as positive, in participants achieving serum uric acid <6.0mg/dl after 24 weeks of trial.
Results: Mean age of the patients was 51.57±20.38 years. Gender distribution shows that 54(77.1%) patients were male while 16 (22.9%) patients were female. Out of total 35 patients in febuxostat group, efficacy was found in 23 (65.7%) patients and among 35 patients of allopurinol group, efficacy was found in 15(39.5%) patients. Chi-square test was applied to compare the efficacy in both of the two groups and a significant difference was found (p- 0.055).
Conclusion: It was concluded that efficacy of febuxostat was higher than Allopurinol in lowering the serum uric acid levels in patients with hyperuricemia due to chronic kidney disease.
Keywords: Serum Uric Acid Level, Allopurionol, Febuxostat, Hyperuricemia, Chronic Kidney Disease

INTRODUCTION

The frequency of chronic renal diseases (CKD) is increasing all over the world. Raised blood pressure, metabolic syndrome and life style are the major risk factors among the other risk factors of increased incidence of CKD[1]. Raised uric acid level occurs frequently among these patients and is associated with increased cardiovascular disease and progression of their disease[2]. Urate is produced from purine metabolism by our body and is excreted by kidneys[3]. Elevated uric acid can cause gout and formation of renal stones[4]. Uric acid level above 7 mg/dl among males and levels above 6 mg/dl in women are labelled as hyperuricemic. Uric acid in subjected with chronic renal impairment rises parallel to their stage of kidney disease. In patients with CKD stages 1 to 3 prevalence of hyperuricemia is 40-60%, while it is 70% prevalent in CKD stage-IV or stage-V[5]. CKD patients with raised serum urate concentration need pharmacotherapy along with life style modification like diet therapy, increased physical activity and treatment of other comorbidities[6]. The reduction of levels of serum uric acid lesser than saturation point (less than 6.0mg/dl) reduces the rate of gouty attacks, allopurinol has been in practice for several years for this specific reason. In patients with chronic kidney impairment and raised serum urate levels, Allopurinol works as renoprotective agent by inhibiting xanthine oxidase.[7] In spite of its overall effectiveness and safety, it can sometimes lead to potentially fatal conditions like Stevens-Johnson syndrome, liver or renal impairment and severe multisystem hypersensitivity vasculitis[8]. Besides this the condition worsens its extended half-life (ranging 14 to 62 hours) and additional extension of half-life in cases with impaired kidney function.

Febuxostat (a novel oral drug), a non-purine binding xanthine oxidase inhibitor, has recently been introduced to reduced serum urate concentrations, it does not cause Stevens-Johnson syndrome, and the dose modification is not needed in cases with CKD[9]. In the United States, in gout cases, trails were conducted to contrast the efficiency of Febuxostat and Allopurinol. Febuxostat's effectiveness (69%) has been revealed to be much greater contrasted to allopurinol (22%). Febuxostat has a half-life of 4-18 hours (far less compared to allopurinol) and is subjected to hepatic metabolic activities. Reduction in C- reactive protein by this drug leads to decline in kidney disease progression in CKD subjects[10]. The goal of the research was to assess the effectiveness of allopurinol and febuxostat in decreasing the levels of uric acid caused by chronic renal disease among cases with hyperuricemia. In Pakistan, No clinical trial was found regarding comparison of the effectiveness of febuxostat and allopurinol in urate reduction in cases with hyperuricemia caused by chronic renal disease. This research would generate local data and the drug used for hyperuricemia's pharmacological control in such cases that will demonstrate greater efficacy.

MATERIAL AND METHODS

This Randomized Control Trials study was performed at the Department of Nephrology (OPD), Jinnah postgraduate medical centre, Karachi, from September 2014 to February 2015. Following a prior written consent; 70 subjects fulfilling inclusion criteria such as Stage III or IV chronic renal disease based on the current guidelines of Kidney Disease

Received on 14-02-2019
Accepted on 22-07-2019

Outcome Quality Initiative (KDOQI), aged above 18 years with concentrations of uric acid above 6.8mg dl, and the outpatient department visiting subjects who were previously not treated for hyperuricemia were randomly allocated to two categories by sealed transparent envelops. After a written consent, patients were required to select an envelope that contained group information and so an individual who was not engaged in the research allocated patients to allopurinol (group B) and febuxostat (group A). Subjects with liver dysfunction (serum ALT>52IU/L), alcohol abuse, BMI >35, gout cases, taking prednisolone 10 mg/day, who had history of taking thiazide diuretics and pyrazinamide and patients who were pregnant were excluded from the study. In addition, the patients did not know the group distribution to maintain the research as dual blind. Baseline serum urate was taken in addition to creatinine. Oral febuxostat's daily dose of 240mg and allopurinol's daily dose of 100 mg were administered for 26 weeks. Periodic follow-ups were performed and serum urate concentrations were lastly performed following 24 weeks. Respondents attaining serum uric acid below 6.0mg/dL following 24 weeks of trail were marked as positive. Data analysis was done by SPSS version 17. The mean and standard deviations were presented for age, weight, height and uric acid concentration. Obesity, gender and effectiveness were displayed in the form of frequency and percentage. To contrast the effectiveness in both groups, the Chi-squared test was implemented. The P value was regarded to be significant if it was below 0.05. Effect modifiers were regulated in both groups via stratification of obesity, gender, age, and baseline serum uric acid.

RESULTS

The patient's mean age was 51.57±20.38 years. The lowest and highest age was found 19 and 82 years respectively. In the age groups of 50 and > 50, there were 31(54.3%) and 32(45.7%) patients respectively. The distribution of gender indicated that 54 (77.1%) cases were males whereas females were 16 (22.9%). Obesity was observed in 47 (67.1%) cases, while 27(32.9%) cases were not obese (Table 1).

Table 1: Patients' distribution in terms of age, gender, obesity, height and weight (n=70)

	Frequency	**Percentage**
Age		
50	31	54.3%
>50	32	45.7%
Minimum	19	
Maximum	82	
Mean ± Standard deviation	51.57 ± 20.38 years	
Gender		
Male	54	77.1%
Female	16	22.9%
Obesity		
Yes	47	67.1%
No	27	32.9%
Height		
Mean ± Standard deviation	1.67 ± 0.24 meters	
Weight		
Mean ± Standard deviation	58 ±4.63 kg	

Efficacy In febuxostat group was among 23(65.7%) cases and in the 15(39.5%) cases of allopurinol group. The chi-square test found a significa difference of efficacy among both groups; p-value=0.055 (Table 2).

In cases with level of uric acid around ≤7µmol/L, the efficacy in febuxostat group was seen among 17(60.7%) cases and among 11(39.3%) cases of Allopurinol group. Chi-square test was used and no variance was discovered (p-value 0.081) (Table 3).

In individuals with serum uric acid concentration >7µmol/L, febuxostat group showed efficacy among 6(60%) cases and Allopurinol group showed efficacy among 4(40%) cases. Chi-square test did not show any difference (p-value 0.465) (Table 3).

Table 2: Treament group and efficacy n=70

Efficacy	Group		**Total**	**P-value**
	Allopurinol	**Febuxostat**		
Yes	15 (39.5%)	23 (65.7%)	38 (100%)	
No	20 (62.5%)	12 (37.5%)	32 (100%)	**0.055**
Total	35 (50%)	35 (50%)	70 (100%)	

Table 3: Serum uric acid level ≤7 µmol/L and Efficacy n=31

Efficacy	**Group**		**Total**	**p-value**
	Febuxostat	**Allopurinol**		
Yes	17 (60.7)	11 (39.3)	28 (100)	0.081
No	0 (0)	3 (100)	3 (100)	
Total	17 (54.8)	14 (45.2)	31 (100)	

Table 4: Serum uric acid level >7 µmol/L and Efficacy n=39

Efficacy	**Group**		**Total**	**p-value**
	Febuxostat	**Allopurinol**		
Yes	6 (60)	4 (40)	10 (100)	0.465
No	12 (41.4)	17 (58.6)	29 (100)	
Total	18 (46.2)	21 (53.8)	39 (100)	

DISCUSSION

Allopurinol is prescribed frequently. Even though this medication is very effective, severity and frequency of its side effects demand careful and wise use. Clearly, the advantages of therapy are more significant than the potential risks[11].

Recently, febuxostat has been used in gout which lowers urate by blocking active site on xanthine oxidase. To contrast the efficiency of Febuxostat and Allopurinol in hyperuricemia, multiple trials have been performed in the United States. Febuxostat lessened the uric acid level more than the allopurinol (69% Vs 22%)[12]. Febuxostat is metabolized by liver with half-life of 4-18 hours (much lower than allopurinol)[13].

The effectiveness of Febuxostat over Allopurinol has been described in many studies. Becker MA et al, reported a better efficacy of Febuxostat than allopurinol, at 80 to 120 mg per day than at a fixed and frequently practiced dose of 300 mg per day. Same results were observed in reducing tophus area and gout flares among every treatment group[14].

The Allopurinol versus Febuxostat Controlled Trial (FACT) was a multicenter clinical, double-blind, 52-week randomized trial that contrasted the efficacy and safety of both drugs. To keep uric acid level at 6.0mg/dl on every 3-month visit was the primary endpoint. The endpoint stated above was accomplished more widely in subjects taking

febuxostat than the allopurinol (53% and 62% cases in the febuxostat group at the daily dose of 80mg and 120mg respectively, and 21% cases in the allopurinol group at 300mg per day); (*P* 0.001). Decrease in uric acid level from baseline and percentage of cases with uric acid of 6mg/dl on each visit was the secondary endpoints. Patients who were on febuxostat met these endpoints more than the patients taking allopurinol. The author found that febuxostat had a considerably greater reduction in uric acid endpoints than allopurinol; however, clinical outcomes exhibited no variance among the both drugs[15].

In allopurinol users, a significant decline was seen in mean level of uric acid from 8.7 to 7.1mg/ dl, with a P value of <0.001. The non-achieving of target levels of uric acid about<6.0mg/dl can possibly be attributed to unawareness of ideal uric acid level, compliance, efficacy and allopurinol dosing. Patients who failed to attain SUA were at enhanced danger of flare[16].

In this research, effectiveness was found in 23(65.7%) patients out of overall 35 cases in febuxostat group and in 15(39.5%) patients out of 35 patients in the allopurinol group. Chi-square testing was used to contrast the effectiveness in both groups and a distinction was discovered (p-0.055).

The Allopurinol-Placebo-controlled febuxostat efficacy research was a double-blind, 28-week, randomized study contrasting the effectiveness and safety of allopurinol, febuxostat, and placebo. The writer found that febuxostat met reducing endpoints for uric acid considerably higher than placebo and allopurinol[17].

CONCLUSION

It was concluded that the febuxostat was effective than Allopurinol in lessening the levels of uric acid among the hyperuricemia patients because of chronic renal disease.

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