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ORIGINAL ARTICLE

USE OF ALLOPURINOL IN SLOWING THE PROGRESS OF CHRONIC KIDNEY DISEASE STAGE III AND IV

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Abstract:

Background: *Hyperuricemia is associated with the event of hypertension and renal disease progression. The aim of the study was to evaluate the role of allopurinol in slowing the progression of chronic kidney disease (CKD) stage III and IV.* ***Methods:*** *This study was prospective interventional study was carried out in department of Nephrology, Sir Salimullah Medical College and Mitford Hospital, Dhaka, during the period of January 2014 to December 2014. On the basis of inclusion and exclusion criteria a total of 80CKD patients were enrolled in this study.80 patients were distributed in two groups. 40 patients were placed in treatment group and 40 patients were placed in control group. Purposive sampling method was followed.40 patients of treatment group were administered allopurinol 100 mg daily. Clinical, hematologic, and biochemical parameters were measured at baseline, at 4th month and 8th month of treatment.* ***Results:*** *No significant differences were seen between baseline SBP, DBP, Hb and HbA1c with 4th month and 8th follow up in both treatment group and control group. eGFR was significantly less declined at 4th months and 8thmonths in patient treated with allopurinol (treatment group). A negative Pearson's correlation (r= -0.104; p=0.524) was found between uric acid with eGFR at 8th month in treatment group and significant positive Pearson's correlation (r= 0.559 p=0.001) was found with CRP level. eGFR was significantly more declined at 4th months and 8th months in patient of control group. In control group a negative Pearson's correlation (r= -0.126 p=0.437) was found between uric acid with eGFR at 8th month and positive Pearson's correlation (r= 0.275 p=0193) was found with CRP level.* ***Conclusions:*** *Uric acid and CRP were significantly declined at 8th months in treatment group. Thus eGFR progression was significantly slow in treatment group at 4thmonths and 8th months from baseline due to positive effect of allopurinol by reducing inflammatory process that causes by high uric acid.*

Key words: *Allopurinol, Slowing the progress, Chronic kidney disease, Stage III and IV*

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Introduction :

In patients with chronic renal disease, there is decreased uric acid (UA) urinary excretion, and whether it will give rise to hyperuricemia depends on the gastrointestinal excretory compensation. This leads to an increased prevalence of elevated serum UA in patients with chronic kidney disease (CKD) [1]. Elevated serum UA is associated with increased risk for the development of hypertension and cardiovascular disease.[2] Chronic hyperuricemia stimulates the renin-angiotensin system and inhibits the release of endothelial nitric oxide, contributes to renal vasoconstriction and increased BP, as well as to a higher level of interstitial inflammation and progression of renal disease.[3,4]

Allopurinol reduces serum UA levels by inhibiting enzyme xanthine oxidase. For animal models of established renal disease, correction of the hyperuricemic state can significantly improve BP control, reduce proteinuria, and slow the progression of renal disease.[4] There are few information about patients with CKD that confirm these results. The primary objective of this study was to analyze the effects of allopurinol in stage iii and iv CKD patients in reducing the progressing renal disease.

Methods:

The study was approved by the institutional ethics committee, and each participating patient gave written informed consent before enrollment.

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One hundred patients were followed up in Department of Nephrology, Sir Salimullah Medical College and Mitford Hospital from January 2014 to December 2014 and screened for eligibility to participate in the study. Included subjects had to fulfill the following inclusion criteria: (1) Age above 18 years both male and female. (2) CKD stage III (eGFR 30-59 mL/min/1.73 m2) and CKD stage IV (eGFR 15-29 mL/min/1.73 m2) having hyperurecaemia (male>7.6 mg/dl, female>6.0 mg/dl) and (3) Patients who give consent to participate in the study.

We excluded patients with a history of allopurinol hypersentivity, those who were already on allopurinol treatment, with active infections or inflammatory diseases, with HIV infection, with chronic gouty arthritis, and patients who received immuno-suppressive therapy. All patients were distributed in two groups.40 patients were placed in treatment group and 40 patients were placed in control group.

Purposive sampling method was followed. Similar pattern of distribution had been attempted by alternative of the subjects by considering stages of CKD, confounding factors hypertension and diabetes, and treatment history of hypertension, diabetes with similar groups of drugs. Similarly normotensive and nondiabetic patients are placed alternatively in both groups. The dosage of antihypertensive drugs, lipid lowering agents, antiprotienuric drugs and antiplatelet drugs were continued and adjusted according to the individual patient's clinical condition.40 patients of treatment group were administered allopurinol 100 mg daily[5]. Follow up was given two times by four months interval. After collection of data, data were checked and rechecked thoroughly and meticulously to exclude missing or inconsistent data. Corrected data were entered into the computer.

Follow Up Assessment:

During follow up following parameters are investigated of both groups of patient.To determine the effect of allopurinol on inflammatory markers ESR and CRP were measured at baseline, at 4th and 8thmonths of treatment. Serum uric acid was measured similarly to see the effect of allopurinol of all study patients. To determine the effect of allopurinol on renal function and progression of CKD, serum creatinine was measured and eGFR was calculated by using MDRD formula at baseline, at 4th and 8thmonths after starting treatment. Clinical and biochemical findings were compared between control group and with that of the treatment group.

Results:

Table I

Distribution of study population by demographic variable (n=80)

Age (years)	Treatment (n=40)		Control (n=40)		p Value
	n	%	n	%	
11 - 20	1	2.5	0	0.0	
21 - 30	10	25.0	5	12.5	
31 - 40	5	12.5	11	27.5	
41 – 50	9	22.5	4	10.0	
51 - 60	5	12.5	13	32.5	
61 - 70	8	20.0	7	17.5	
71 - 80	2	5.0	0	0.0	
Mean ± SD	44.55±16.97		45.65±12.93		0.091^{ns}
Sex					
Male	28	70.0	26	65.0	0.812^{ns}
Female	12	30.0	14	35.0	

Table I showed that the mean age 44.55±16.97 years in treatment group and 45.65±12.93 years in control group.

Table II

CKD stage of the study population (n=80)

Stage	Treatment (n=40)		Control (n=40)		p Value
	n	%	n	%	
Stage 3	13	32.5	10	25.0	0.458^{ns}
Stage 4	27	67.5	30	75.0	

Table II showed CKD stages of the patients. At CKD Stage-3, 32.5% & 25% were in treatment & control group respectively. At Stage-4 67.5% & 75%were in treatment & control group respectively.

Table III

SBP & DBP in treatment and control group in CKD Stage 3 and Stage 4 (n=80)

	Treatment(n=40)	Control(n=40)	p Value
SBP (mmHg)	Mean±SD	Mean±SD	
Baseline	145.8±8.51	140.7±7.88	0.053^{ns}
At 4th month	139.8±7.33	141.1±8.12	0.063^{ns}
At 8th month	140.6±8.26	140±9.54	0.764 ^{ns}
DBP(mmHg)			
Baseline	86.25±5.96	87.75±8.08	0.347^{ns}
At 4th month	83.88±5.94	85.75±7.64	0.225 ^{ns}
At 8th month	81±8.26	82.18±10.18	0.507 ^{ns}

Table III showed no significant change in SBP & DBP was observed in treatment group and control group after 8th month of the study.

Table IV

Effect of allopurinol on Inflammatory marker in treatment and control group in CKD Stage 3 and Stage 4 (n=80)

	Treatment (n=40) Mean±SD	Control (n=40) Mean±SD	p Value
ESR			
Baseline	38.3±13.23	41.77±11.61	0.089^{ns}
At 4th month	32.65±9.49	42.69±10.65	0.001 ^{s}
At 8th month	27.93±7.69	40.23±9.73	0.011^{s}
CRP (mg/L)			
Baseline	15.5±8.88	16.53±11.92	0.831 ^{ns}
At 4th month	12.03±8.28	18.8±13.41	0.008^{s}
At 8th month	10.78±6.65	21.1±15.26	0.001^{s}

Table VII showed, inflammatory marker was reduced in treatment group at 4th&8th month of follow up but was increased in control group in both follow up compare to the baseline.

Table V

Effect of allopurinol on Uric Acid in treatment and control group in CKD Stage 3 and Stage 4 (n=80)

	Treatment (n=40) Mean±SD	Control (n=40) Mean±SD	p Value
Serum uric acid (mg/dl)			
Baseline	9.16±1.04	9.07±0.97	0.691 ^{ns}
At 4th month	8.41±0.88	9.47±0.97	0.001^{s}
p value	0.001^{s}	0.001^{s}	
At 8th month	7.79±0.65	9.85±0.91	0.001^{s}
p value	0.001^{s}	0.001^{s}	

Table IX showed, serum uric acid was decreased in treatment group and increased in control group at 4th month and 8th month of follow up compare to the baseline. There was significant change observed in serum Uric Acid level between treatment and control group.

Table VI

Effect of allopurinol on Creatinine in treatment and control group in CKD Stage 3 and Stage 4 (n=80)

	Treatment (n=40) Mean±SD	Control (n=40) Mean±SD	p Value
Serum creatinine (mg/dl)			
Baseline	3.02±0.80	2.86±0.72	0.350 ^{ns}
At 4th month	3.03±0.81	3.11±0.81	0.659^{ns}
p value	0.327^{ns}	0.001^{s}	
At 8th month	3.03±0.81	3.31±0.87	0.140^{ns}
p value	0.266^{ns}	0.001^{s}	

Table VI showed, after 8th month follow up, S Creatinine was remained stable in patients treated with Allopurinol and was reduced in patients without Allopurinol treatment compare to the baseline. But there was no significant difference in S Creatinine (p<0.001) between treatment and control group.

Table VII

Effect of allopurinol on eGFR in treatment and control group in CKD Stage 3 and Stage 4 (n=80)

	Treatment (n=40) Mean±SD	Control (n=40) Mean±SD	p Value
eGFR			
Baseline	24.27±7.33	25.28±7.99	0.557^{ns}
At 4th month	24.16±7.37	23.04±7.82	0.512 ^{ns}
p value	0.442^{ns}	0.001^{s}	
At 8th month	24.20±7.45	21.45±7.25	0.098^{ns}
p value	0.477^{ns}	0.001^{s}	

Table VII showed after 8th month follow up, eGFR was remained stable in patients treated with Allopurinol and was reduced in patients without Allopurinol treatment compare to the baseline. But there was no significant difference in eGFR (p<0.001) between treatment and control group.

Discussion:

Hyperuricemia is common in patients with CKD due to decreased uric acid excretion. Allopurinol inhibits the production of serum Uric Acid. This prospective interventional study was done with an aim to see serum Uric Acid lowering effect of Allopurinol in CKD Stage 3 and Stage 4 patients and to see the slowing progression of CKD at a regular interval in treatment group.

A total of 100 CKD patients were enrolled in this study, 40 patients were placed in treatment group and 50 patients were placed in control group. 40 patients of treatment group were administered allupurinol 100 mg daily along with conventional treatment.

In this current study it was observed that one fourth (22.0%) patients belonged to age 21 – 30 years in treatment group and 12.5% in control group. The mean age was 44.55±16.97 years in treatment group and 45.65±12.93 years in control group. The mean age difference was almost the same between the two groups.Paietal.found the mean age was of the allopurinol group was 50.15±14.42 years and control group was 53.23±13.86 years, which is a little higher with the current study. [6]

In this present study it was observed that male subject was predominant in both groups, where 70.0% and 65.0% patients were male in treatment group and control group respectively. Similar observations regarding the male predominant were also found by Sakai et al. and Goicoechea et al. [5, 7].

In this study showed that at CKD Stage-3, 32.5% & 25% were in treatment & control group respectively. At Stage-4 67.5% & 75%were in treatment & control group respectively. Which is differ with the current study.

In this present study it was observed that no significant difference between baseline means of SBP and DBP at 4th months and at end of the study between treatment and control group (p>0.05). There was no significant change in SBP and DBP were observed in the treatment group and control group after 8th month of the study.

In the study Satirapojet al.[7]mentioned in their study that allopurinol had statistically significant lower systolic BP (137.72 ± 14.72 to 131.34 ± 12.10 mmHg, p<0.05) and diastolic BP (79.63 ± 11.56 to 75.43 ± 9.80 mmHg, p<0.05) at 12 weeks when compared to baseline. It is dissimilar with the current study.

To determine the effect of allopurinol on inflammatory markers in treatment group and control group in this series it was observed that ESR and CRP (mg/l) were significantly higher in control group at 4th month and end of the study.CRP and ESR were reduced in treatment group at 8thmonth of follow up but was increased in control group in both follow up compare to the baseline. There was significant change observed in CRP and ESR between treatment and control group. Goicoecheaet al.[5]study suggested that a benefit from lowering C-reactive protein (CRP) level and ESR in patients treated with Allopurinol.

In this study it was observed that the effect of allopurinol on UA levels and renal function in treatment group and control group, serum creatinine and serum uric acid level was significantly higher in control group at end of the study. Uric Acid was significantly decreased in treatment group and was increased in control group at 4th months and 8th months of follow up, in CKD stage 3 and stage 4, compare to the baseline. Goicoechea et al.study showed after 24 months of Allopurinol treatment, serum UA levels were significantly decreased in subjects treated with Allopurinol.[5]

In this present study, there was no significant change in serum creatinine levels in treatment group at 4th and 8th month follow up in CKD stage III and CKD stage IV,compare to the baseline. Whereas, there was significant increased or worsening in the control group in both follow up in CKD stage 3 and CKD stage 4, compare to baseline.

In this present study, there was no significant change in eGFR in treatment group at 4th and 8th month follow upcompare to the baseline in CKD stage 3 and CKD stage 4 .Whereas ,there was significant declined or worsening of eGFR in the control group.

In study Siu et al.observed that serum creatinine levels in hyperuricemic patients with mild to moderate chronic kidney disease taking allopurinol display a declining trend within 12 months, although they did not see a significant difference, compared to the control group. [8]

However, despite the work done thus far in hyperuricaemia and its effects on hypertension and potential effects on mortality, the 2012 Kidney Disease Improving Global Outcomes practice guidelines for the evaluation and management of chronic kidney disease state that there is insufficient evidence to recommend the use of medications such as allopurinol to delay the progression of CKD.

Conclusions:

Allopurinol reduced inflammatory response by decreasing serum Uric Acid, C Reactive Protein and ESR. At 8th month follow up, renal function was remained stable in patients treated with Allopurinol and was worsened in patients without Allopurinol treatment. So, Allopurinol may have a protective role in chronic kidney disease progression.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study

Funding:

No specific funding was received for this study.

Ethical consideration:

The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained.

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