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Research Article

Clinical evaluation of efficacy and safety of α-keto analogs of essential amino acids supplementation in patients of chronic kidney disease

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ABSTRACT

Background: The objective was to evaluate the efficacy and safety of α-keto analogs of essential amino acids (KAA) as a supplement in chronic kidney disease (CKD).
Methods: A prospective comparative study was conducted in patients of CKD of a tertiary care center of North India. Patients were randomly divided into two interventional groups. Group I (control) was advised conservative management and placebo while Group II (KAA) given conservative management along with KAA (600 mg, thrice daily) for 12 weeks. Hemogram, renal function tests, lipid profiles were done, and adverse effects were recorded at 0, 4, 8, and 12 weeks of treatment.
Results: There was progressive improvement in clinical features in both groups after 12 weeks of treatment, but KAA group showed more marked improvement as compared with the control group. Both groups showed gradual improvement in the biochemical parameters as compared to their pre-treated values, which was more marked in KAA supplemented group. There was a reduction in blood glucose, blood urea, serum creatinine, and 24 h total urine protein. There was an increase in hemoglobin, 24 h total urine volume and glomerular filtration rate. KAA group showed significant ($p<0.05$) improvement in lipid profiles as compared with the control group. There was no statistical difference in two groups with respect to side-effects ($p>0.05$).
Conclusion: KAA supplementation along with conservative management is efficacious and safe in preventing the progression of disease in patients of CKD.

Keywords: Keto amino acids, Glomerular filtration rate, Conservative management, End stage renal disease

INTRODUCTION

Chronic kidney disease (CKD) is a public health problem worldwide.[1] According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines,[2] CKD is defined as: kidney damage or glomerular filtration rate (GFR)<60 ml/min/1.73 m^2 for 3 months or more, irrespective of the cause. The prevalence of CKD in Screening and Early Evaluation of Kidney Disease (SEEK)-India cohort was approximately 17.2% with ~6% have CKD stage 3 or worse.[3] The financial burden of renal replacement therapy (RRT) is increased with increasing prevalence of CKD; CKD related CVD and end stage renal disease (ESRD). It is estimated that around 100,000 new patients of ESRD require RRT annually in India.[4] Low protein diet (LPD) (0.6 g/kg BW/day) as well as very low protein diet (VLPD) (0.3 g/kg BW/day) decreases the accumulation of nitrogen waste products while maintaining an adequate nutritional status. Hence, secondary problems such as metabolic acidosis, bone disease and insulin resistance, as well as proteinuria and deterioration of renal function are reduced.[5,6]

α-Keto analogs of essential amino acids/keto amino acids (KAA) are nitrogen free analogs of essential amino acids. The use of KAA in association with a LPD or VLPD allows a reduced intake of nitrogen, while avoiding the deleterious consequences of inadequate dietary protein intake and malnourishment.[5,7-12] The aim of our study was to evaluate the efficacy and safety of KAA supplementation in patients of CKD.

METHODS

Patients

The present study was conducted from June 2012 to September 2013 in patients of CKD attending Renal Clinic or admitted in IPD of a tertiary care center of North India. It was a randomized, prospective, double-blinded, and parallel group study. The approval for the study was taken Institutional Ethics Committee, J.N. Medical College, A.M.U. Aligarh. The study is registered under Clinical Trial Registry of India with registration number CTRI/2012/09/002947 (Registered on: 03/09/2012). Written and informed consent was taken from all patients before enrolling in the study. The diagnosis of CKD was made on the basis of detailed clinical history, physical examination, and investigations (renal function tests).

The diagnostic criteria for CKD according to the National Kidney Foundation's K/DOQI guidelines (2002)[13] is: kidney damage for ≥3 months or GFR <60 ml/min/1.73 m^2 for ≥3 months with or without kidney damage.

Inclusion criteria

Patients having CKD (stage 3-4), age 20-60 years and of either sex were included in the study.

Exclusion criteria

Patients of ESRD, on dialysis, pregnant, terminally ill, immunocompromised or severe renal pathology such as malignancy were excluded from the study.

Sample size (n)

$n=(z^2/e^2)$ pq, where z=level of the confidence interval at 95%, so z=1.96; e=acceptable error; p=prevalence (prevalence assumed as 17.2% according to SEEK-India cohort study);[3] q=1-p. Hence, sample size (n)=[(1.96*1.96)/(0.09*0.09)]*[0.172*0.828]=67.54. Hence, sample size of 68 is minimum required for each group. Taking into consideration a 15% dropout rate, 80 patients were recruited in each group.

Study design

Of 180 assessed patients, 160 patients were enrolled in the study. Fifteen patients (9 of Group I and 6 of Group II) failed to report on subsequent visits and were excluded from the study. Enrolled patients were randomized into two groups at a ratio of 1:1 using table generated by random allocation software. The randomization table had 20 subjects in each block to minimize the disparity between the three groups with respect to the number of patients at any time of study. After final diagnosis, applying inclusion and exclusion criteria, patients were included in the study. Group I (control) patients received conservative management of CKD along with placebo while Group II (KAA) patients received conservative management of CKD along with KAA tablet (600 mg) thrice daily (Figure 1). Both groups received treatment for 12 weeks. In conservative management treatment given was renal diet and telmisartan (40 mg once daily). KAA contains α-keto analogs of DL-isoleucine, leucine, phenylalanine, valine, DL-methionine, L-lysine acetate, L-threonine, L-tryptophan, L-histidine, L-tyrosine as their calcium salts.

All the enrolled patients were regularly followed with hemogram, renal function tests, and lipid profile tests at 0, 4, 8, and 12, weeks of treatment.

Safety assessments

All adverse events experienced by a patient or observed by the investigator were recorded on standard adverse drug reaction (ADR) reporting forms of CDSCO at each visit. ADRs causality assessment was done using Naranjo Scale[14] and severity assessment by Modified Hartwig & Siegel Scale.[15] A physical examination, including vital signs, was performed at the start of study and at each visit. Additional routine laboratory safety test such as liver function tests (LFT), electrocardiography, and chest X-ray were performed wherever required. All the ADRs were reported to the ADR monitoring center of the college.

Statistical analysis

The values were expressed as mean ± SD. Statistical significance between pre- and post-treatment values in each group was calculated using Student's paired t-test. Statistical significance between groups was calculated using unpaired t-test. $p<0.05$ was considered to be significant. Statistical analysis was done using SPSS-20 software.

RESULTS

Seventy-one (41 M, 30 F) patients mean aged 45 years (range 22-58 years) were of Group I and 74 (44 M, 30 F) patients mean aged 45 years (range 21-59 years) were of Group II. The distribution of patients was almost similar in both groups. None of the patient in either group required dialysis, and there was no mortality in either group. As per GFR (mL/min/1.73 m^2), patients belonged to stage 3 (19 and 22 in Groups I and II, respectively) and stage 4 (52 in each group) CKD in both groups. The causes of CKD in Groups I and II were: diabetic nephropathy (45.07% and 43.24%), hypertensive nephropathy (18.30% and 20.27%), chronic glomerulonephritis (11.26% and 10.81%), tubulointerstitial nephritis (8.45% and 5.40%), autosomal dominant polycystic kidney disease (4.22% and 5.40%) and unknown cause (12.67% and 14.86%).

In the present study, the clinical features found in patients at admission were: anorexia, nausea, vomiting, weakness,

weight loss, and headache, pruritus, swelling over body, oliguria, anemia, hypertension, and dyspnea. The clinical features were almost similar at 0 week in both groups. There was gradual improvement in clinical features in both groups after 12 weeks of treatment, but it was more marked in KAA group.

There was progressive decrease in both systolic and diastolic blood pressure toward normal in both groups. As compared with the control group, KAA group showed significant ($p<0.05$) reduction in both systolic and diastolic blood pressure after 12 weeks of the treatment (Table 1).

There was progressive improvement in lipid profile after 12 weeks in both groups, which was significant ($p<0.05$) in KAA group as compared with control (Table 1).

The total leukocyte count, differential leukocyte count, and platelet count remained within normal limits at the end of 12 weeks of treatment in both groups.

There was progressive improvement in various biochemical parameters in both groups; KAA group showed maximum improvement. As compared with the control group, KAA group showed a significant increase in hemoglobin percent ($p<0.05$), decrease in fasting and post-prandial blood glucose ($p<0.001$), decrease in blood urea ($p<0.001$) and decrease in serum creatinine ($p<0.05$) at 12 weeks. There was a progressive increase in serum sodium in both groups, which was statistically not significant; however, there was a decrease in serum potassium in both groups, which was significant ($p<0.001$) in KAA group as compared with control. There was a significant increase in serum calcium ($p<0.001$), decrease in total urine protein ($p<0.01$), increase in total urine volume ($p<0.001$) and increase in GFR ($p<0.001$) after 12 weeks of treatment in KAA group as compared with the control group (Table 2).

The ADRs occurrence was not significantly different between control and KAA groups. According to Modified Hartwig & Siegel Scale, the ADRs were mild (no hospitalization, no change of therapy and no additional treatment) in severity in both groups. No adverse event was of acute onset (within 60 min). On Naranjo's Scale, the ADRs were possible (Score = 1-4) in 12 cases and probable (Score = 5-8) in 11 cases with the control group while possible (Score = 1-4) in 15 cases and probable (Score = 5-8) in 7 cases with KAA group (Table 3).

DISCUSSION

CKD is an emerging chronic disease globally due to rapidly increasing incidence of diabetes and hypertension worldwide.[16,17] CKD leads to premature morbidity and mortality and hampers quality of life. In India, CKD is a major problem for both health sector and economy. The ideal treatment for CKD-ESRD is RRT which includes renal transplantation and maintenance dialysis. More than 100,000 new patients enter RRT annually in India.[18] Because of meager resources, only 10% of Indian ESRD patients receive any RRT. The monthly cost of hemodialysis is $300, whereas continuous ambulatory peritoneal dialysis costs $600. The cost of transplant is $8900 in the 1st year, which declines later to $3000 annually. Among the RRT options, renal transplant is the preferred choice as it is cost-effective and offers better quality of life, but still only a fraction of Indians can afford it.[18]

Table 1: Blood pressure and lipid profile tests in control and KAA groups before and after 12 weeks of treatment.

Parameter	Group	0 week mean±SD	12 weeks mean±SD	Percentage change after 12 weeks
SBP (mm Hg)	I	150.40±17.62	136.62±16.45^{b}	(−) 9.16
	II	156.78±22.86	130.85±9.58^{c1}	(−) 16.53
DBP (mm Hg)	I	87.32±10.43	85.98±9.65	(−) 1.53
	II	88.02±12.40	83.80±10.71^{c1}	(−) 4.79
T.Ch. (mg/dL)	I	196.46±29.83	191.99±23.24^{a}	(−) 2.27
	II	197.27±29.03	185.18±22.42^{c1}	(−) 6.12
TG (mg/dL)	I	130.89±21.52	120.28±20.98^{a}	(−) 8.10
	II	132.17±19.94	112.50±18.68^{c1}	(−) 14.88
HDL (mg/dL)	I	48.00±5.81	49.13±7.47^{b}	(+) 2.35
	II	46.44±5.69	49.33±7.26^{c1}	(+) 6.62
LDL (mg/dL)	I	130.82±23.01	129.13±17.86^{a}	(−) 1.29
	II	132.30±21.72	125.02±16.88^{c1}	(−) 5.50
VLDL (mg/dL)	I	16.45±2.75	14.82±2.17^{b}	(−) 9.90
	II	15.63±1.99	13.70±1.73^{c1}	(−) 12.34

Values are mean±SD, $p<0.05$ was considered significant, a: $p<0.05$, b: $p<0.01$, c: $p<0.001$ compared to 0 week value of respective group, 1: $p<0.05$, 2: $p<0.01$, 3: $p<0.001$ compared to control group, I: Control, II: KAA, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, T.Ch.: Total cholesterol, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein, −: Decrease, +: Increase, KAA: Keto analogs of essential amino acids

Table 2: Haemogram and renal function tests in control and KAA groups before and after 12 weeks of treatment.

Parameter	Group	0 week mean±SD	12 weeks mean±SD	Percentage change after 12 weeks
Hb % (g/dL)	I	7.91±1.93	8.91±1.48^{c}	(+) 12.64
	II	7.84±1.10	9.39±0.87^{c1}	(+) 19.77
FBG (mg/dL)	I	130.05±42.90	113.78±14.3^{1c}	(−) 12.51
	II	131.28±44.31	104.00±8.46^{c3}	(−) 20.78
PPBG (mg/dL)	I	184.95±61.17	157.56±23.20^{c}	(−) 14.80
	II	181.28±55.22	143.40±12.83^{c3}	(−) 20.89
B.Urea (mg/dL)	I	107.16±35.85	79.78±24.79^{b}	(−) 25.55
	II	106.73±27.72	66.07±19.29^{c3}	(−) 38.09
S.Cr. (mg/dL)	I	4.44±1.64	3.33±1.37^{c}	(−) 25.00
	II	4.68±1.86	2.83±1.10^{c1}	(−) 39.52
K^+ (mEq/L)	I	4.87±0.49	4.63±0.41^{a}	(−) 4.92
	II	4.80±0.46	4.22±0.44^{c3}	(−) 12.08
Ca^{2+} (mg/dL)	I	8.65±1.05	8.89±1.00^{a}	(+) 2.77
	II	8.70±1.11	9.54±0.91^{c3}	(+) 9.65
TUP (g/day)	I	3.03±1.29	2.43±0.97^{b}	(−) 19.80
	II	3.34±0.88	2.06±0.61^{c2}	(−) 38.34
TUV (mL/day)	I	1454.36±221.53	1736.76±176.04^{c}	(+) 19.41
	II	1457.46±179.48	1943.23±204.1^{c3}	(+) 33.32
GFR (mL/min)	I	19.0±1.17	23.3±1.63^{b}	(+) 22.6
	II	19.7±1.86	29.4±3.68^{c3}	(+) 49.2

Values are mean±SD, p<0.05 was considered significant, a: p<0.05, b: p<0.01, c: p<0.001 compared to 0 week value of respective group, 1: p<0.05, 2: p<0.01, 3: p<0.001 compared to control group, I: Control, II: KAA, Hb %: Hemoglobin percent, FBG: Fasting blood glucose, PPBG: Postprandial blood glucose, B. Urea: Blood urea, S. Cr.: Serum creatinine, K^+: Serum potassium, Ca^{2+}: Serum calcium, TUP: 24 h Total urine protein, TUV: 24 h total urine volume, GFR: Glomerular filtration rate, −: Decrease, +: Increase, KAA: Keto analogs of essential amino acids

Table 3: Comparison of adverse drug reactions (ADRs) between Control and Keto amino acid group.

ADR recorded	Control (n=71)	KAA (n=74)	Significance (2-tailed)
Nausea	5	3	0.494
Vomiting	4	2	0.442
Diarrhea	5	2	0.275
Constipation	0	2	0.497
Anorexia	4	3	0.719
Excessive thirst	0	3	0.245
Abdominal pain	1	2	1.000
Muscle and joint pain	0	1	1.000
Headache	3	1	0.366
Rashes	0	1	1.000
Altered taste	0	1	1.000
Weakness	1	0	0.497
Frequent urination	0	1	1.000

p<0.05 was considered significant; Fisher's exact test was applied. KAA: Keto analogs of essential amino acids

Conservative management is very important to prevent CKD and to prevent progression of CKD to ESRD. It delays the progressive deterioration of renal function. It provides only symptomatic relief. Hence, newer treatment modalities are being searched, which can halt nephron damage, delay the development of ESRD, and cost-effective.

Richards et al. suggested that KAA might be useful in the treatment of uremia.[19] According to Teplan, KAA get transaminated by taking nitrogen from non-essential amino acids, thereby decreasing the formation of urea by re-using the amino group.[8] Ketoacids reduce protein degradation and urinary protein excretion. Ell et al. showed that ketoacid supplements produced a reduction of plasma urea, urea synthesis and urea excretion and an improvement in nitrogen balance in patients of chronic renal failure.[20] KAA had good glycemic control, improved insulin sensitivity and reduced hyperinsulinemia.[9] Chen et al. showed a significant reduction in tumor necrosis factor-α, C-reactive protein and adiponectin on keto acid supplementation in type 2 diabetic nephropathy.[21] These might be the probable mechanisms for beneficial effects of KAA in our study.

Di Iorio et al. showed that supplementation of KAA along with LPD in CKD patients resulted in a reduction of about 35% of the erythropoietin dose required to maintain the target hemoglobin levels.[22] In moderate to advanced CKD, VLPD has an antihypertensive effect likely due to

reduction of salt intake, type of proteins, and keto analogs supplementation, independent of actual protein intake.[23] A VLPD supplemented with keto analogs reduced fibroblast growth factor 23 levels in CKD patients not yet on dialysis.[24] Phosphate is an important modifier of the anti-proteinuric response to VLPD. Reducing phosphate burden, KAA may decrease proteinuria and slow the progression of renal disease in CKD patients.[25] High levels of indoxyl sulfate (IS) are associated with chronic kidney disease (CKD) progression and increased mortality in CKD patients. VLPD supplemented with keto analogs reduced IS serum levels in CKD patients not yet on dialysis.[26] Garneata et al. showed that VLPD supplemented with KAA proved effective in delaying the initiation of dialysis without deleterious effects on nutritional status.[27] In 2013, there was a consensus of many experts that keto-acid therapy in predialysis chronic kidney disease patients is an essential part of therapy.[28] The results of our study showed the beneficial effect of KAA on various parameters. Furthermore, none of the study was done on Indian population. Hence, our study showed the beneficial effect of KAA in patients of CKD from India.

KAA showed beneficial effects in CKD stage 4, 5 at a dose of 60 mg/kg BW/day.[10] Hence, KAA dose used in our study was 600 mg 3 times daily.

Walser et al. showed that KAA supplementation at a dose of 6-14 g/day for 15-60 days in 10 patients of severe uremia produced no toxicity.[11] Mitch et al. they found no side-effect or toxicity of KAA supplementation in patients of CKD.[12] Hence, the ADRs might be the manifestations of underlying renal pathology or due to other co-administered drugs.

The findings in our study are in accordance with those reported in previous studies. Hence, supplementation of KAA along with conservative management produces improvement in clinical features as well as biochemical parameters and safe in patients of CKD.

CONCLUSION

KAA supplementation improved the therapeutic effect of conservative management in patients of CKD.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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