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Original Article

A RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF α-KETO AMINO ACIDS IN STAGE 3 AND 4 OF CHRONIC KIDNEY DISEASE

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ABSTRACT

Objective: To evaluate efficacy and safety of α-Keto analogues of essential amino acids (KAA) in stage 3 and 4 patients of Chronic Kidney Disease.

Material and Methods: The study was conducted in stage 3 and 4 patients of Chronic Kidney Disease of a tertiary care centre of north India. It was a prospective comparative study. Patients were randomly divided into two interventional groups. Group I (Control) received conservative management and placebo while Group II (KAA) was managed on conservative management along with KAA (600 mg, thrice daily) for 12 weeks. Haemogram and renal function tests 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 the groups after 12 weeks of treatment but KAA group showed more marked improvement as compared to 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 reduction in blood glucose, blood urea, serum creatinine and 24 hour total urine protein (TUP). There was increase in haemoglobin, 24 hour total urine volume (TUV) and glomerular filtration rate (GFR). There was no statistical difference in two groups with respect to side effects ($p>0.05$).

Conclusion: α-Keto analogues of essential amino acids (KAA) supplementation along with conservative management is efficacious and safe in preventing the progression of disease in stage 3 and 4 patients of Chronic Kidney Disease.

Keywords: Chronic Kidney Disease, Keto amino acids, conservative management, End stage renal disease.

INTRODUCTION

According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines,[1]Chronic Kidney Disease is defined as: kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 $m^2$for 3 months or more, irrespective of cause. Chronic kidney disease (CKD) is a public health problem worldwide. [2]The prevalence of CKD in 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 1,00,000 new patients of ESRD require RRT annually in India.[4]Low protein diet (0.6 g/kg BW/day) as well as very low protein diet (0.3 g/kg BW/day) decreases the accumulation of nitrogen waste products while maintaining an adequate nutritional status. So, 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 analogues of essential amino acids / Keto amino acids (KAA) are nitrogen free analogues of essential amino acids. The use of KAA in association with a low or very low protein diet allows a reduced intake of nitrogen while avoiding the deleterious consequences of inadequate dietary protein intake and malnourishment.[5,7,14,16,18,19,20]The aim of our study was to evaluate the efficacy and safety of α-Keto analogues of essential amino acids (KAA) supplementation in patients of Chronic Kidney Disease.

MATERIAL AND METHODS

Patients

The present study was conducted from June 2012 to September 2013 in patients of Chronic Kidney Disease attending Renal Clinic or admitted in IPD of a tertiary care centre of north India. It was a randomized, prospective, double blinded and parallel group study. The approval for the study was taken from Institutional Ethics Committee. 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).

Inclusion criteria

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

Exclusion criteria

Patients on dialysis, pregnant, terminally ill, immuno-compromised 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 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. So, 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

Out 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 1:1using table generated by random allocation software. The randomization table had 20 subjects in each block to minimize the disparity between the two groups with respect to 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 OD). KAA contains α-keto analogues 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 haemogram, renal function tests and lipid profile tests at 0, 4, 8 and 12 weeks of treatment.

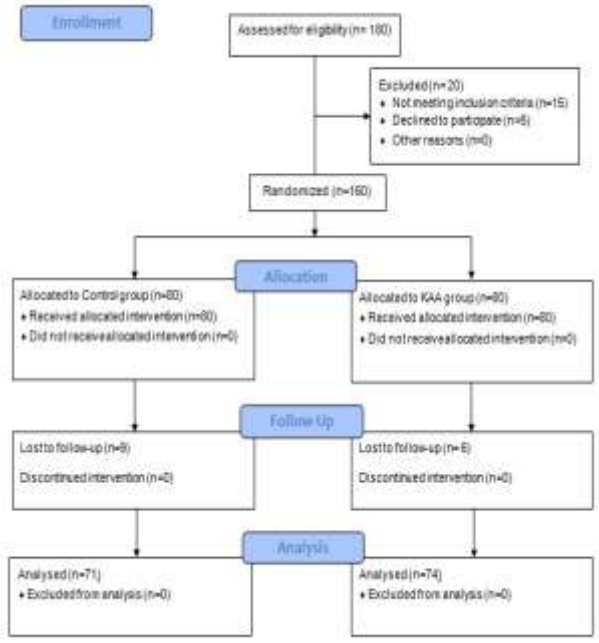

Fig.1: It showsrecruitment, allocation and follow-up of participants.

Safety Assessments

All adverse events experienced by a patient or observed by the investigator were recorded on standard ADR reporting forms of CDSCO at each visit. Adverse drug reaction's causality assessment was done using Naranjo Scale[8] and severity assessment by Modified Hartwig & Siegel Scale.[9] A physical examination, including vital signs, was performed at the start of study and at each visit. Additional routine laboratory safety test like liver function tests (LFT), ECG and Chest X ray were performed wherever required. All the ADRs were reported to the ADR monitoring centre 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 significant. Statistical analysis was done using SPSS-20 software.

RESULT

71 (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 the groups. None of the patient in either group required dialysis and there was no mortality in either group. As per GFR (mL/min per 1.73 m^2), patients belonged to stage 3 (19 and 22 in Group I and II respectively) and stage 4 (52 in each Group) CKD in both the groups. The causes of CKD in group 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 the patients at admission were: anorexia, nausea, vomiting, weakness, weight loss, headache, pruritus, swelling over body, oliguria, anaemia, hypertension and dyspnoea. The clinical features were almost similar at 0 week in both the groups. There was gradual improvement in clinical features in both the groups after 12 weeks of treatment but it was more marked in KAA group.

There was progressive improvement in various biochemical parameters in both the groups; KAA group showed maximum improvement. As compared to control group, KAA group showed significant increase in haemoglobin 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 decrease in serum potassiumin both the groups, which was significant ($p<0.001$) in KAA group as compared to control. There was significant increase in serum calcium ($p<0.001$), decrease in TUP ($p<0.01$), increase in TUV ($p<0.001$) and increase in GFR ($p<0.001$) after 12 weeks of treatment in KAA group as compared to control group (Table 1).

The adverse drug reactions occurrence was not significantly different between control and KAA groups. According to Modified Hartwig & Siegel Scale, the adverse drug reactions were mild (no hospitalization, no change of therapy and no additional treatment) in severity in both the groups. No adverse event was of acute onset (within 60 minutes).On Naranjo's Scale, the ADRs were possible (Score = 1-4) in 12 cases and probable (Score = 5-8) in 11 cases with control group while possible (Score = 1-4) in 15 cases and probable (Score = 5-8) in 7 cases with KAA group (Table 2).

DISCUSSION

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. So, newer treatment modalities are being searched which can halt nephron damage, delay the development of ESRD and cost effective.

Chronic kidney disease (CKD) is an emerging chronic disease globally due to rapidly increasing incidence of diabetes and hypertension worldwide.[10,11] 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 Renal Replacement Therapy (RRT) which includes renal transplantation and maintenance dialysis. More than 100,000 new patients enter RRT annually in India.[12]Because of meagre resources, only 10% of Indian ESRD patients receive any RRT. The monthly cost of hemodialysis is $300, whereas CAPD costs $600. The cost of transplant is $8900 in the first year, which declines later to $3000 annually. Among the RRT options, renal transplant is the pre-ferred choice as it is cost effective and offers better quality of life but still only a fraction of Indians can afford it.[12]

Richards P et al suggested that α-keto-analogues of the essential amino acids might be useful in the treatment of uremia.[13] According to Teplan V, KAA get transaminated by taking nitrogen from non-essential amino acids, thereby decreasing the formation of urea by re-using the amino group.[14] Ketoacids reduce protein degradation and urinary protein excretion. Ell S et al showed that keto-acid supplements produced reduction of plasma urea, urea synthesis and urea excretion and an improvement in nitrogen balance in patients of chronic renal failure.[15]KAA had good glycemic control, improved insulin sensitivity and reduced hyperinsulinemia.[16] Chen N et al showed significant reduction in TNF-α, CRP and adiponectin on keto acid supplementation in type 2 diabetic nephropathy.[17]These might be the probable mechanisms for beneficial effects of KAA in our study.

KAA showed beneficial effects in CKD stage 4, 5 at dose of 60 mg/kg BW/day.[18]So, KAA dose used in our study was 600 mg TDS daily.

Walser M 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.[19] Mitch WE et al found no side effect or toxicity of KAA supplementation in patients of CKD.[20] So, 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. So, supplementation of α-Keto analogue of essential amino acid along with conservative management produces improvement in clinical features as well as biochemical parameters and safe in patients of Chronic Kidney Disease.

CONCLUSION

α-Keto analogue of essential amino acid supplementation improved the therapeutic effect of conservative management in stage 3 and 4 patients of Chronic Kidney Disease.

Table 1: It shows haemogram and renal function tests in Control and KAA groups before and after 12 weeks of treatment.

S. No.	Parameter	Group	0 week Mean ± SD	12 weeks Mean ± SD	% change after 12 weeks
1.	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%
2.	FBG (mg/dL)	I	130.05±42.90	113.78±14.31^{c}	(-) 12.51%
		II	131.28±44.31	104.00±8.46^{c3}	(-) 20.78%
3.	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%
4.	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%
5.	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%
6.	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%
7.	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%
8.	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%
9.	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%
10.	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 to0 week value of respective group; ^{1}p<0.05, ^{2}p<0.01, ^{3}p<0.001 compared tocontrol group. I=Control; II=KAA; Hb%= Haemoglobin percent; FBG= Fasting Blood Glucose; PPBG= Post-prandial Blood Glucose; B. Urea= Blood Urea; S.Cr.=Serum creatinine; K^{+}= Serum potassium; Ca^{2+}= Serum calcium; TUP=24 Hour Total Urine Protein; TUV=24 Hour Total Urine Volume; GFR = Glomerular Filtration Rate; (-) decrease; (+) increase.

Table 2: It shows comparison of adverse drug reactions (ADRs) between Control and Keto amino acid group.

S.No.	ADR Recorded	Control (n=71)	KAA (n=74)	Significance (2-tailed)
1.	Nausea	5	3	0.494
2.	Vomiting	4	2	0.442
3.	Diarrhea	5	2	0.275
4.	Constipation	0	2	0.497
5.	Anorexia	4	3	0.719
6.	Excessive thirst	0	3	0.245
7.	Abdominal pain	1	2	1.000
8.	Muscle and joint pain	0	1	1.000
9.	Headache	3	1	0.366
10.	Rashes	0	1	1.000
11.	Altered taste	0	1	1.000
12.	Weakness	1	0	0.497
13.	Frequent urination	0	1	1.000

p<0.05 was considered significant. Fisher's Exact Test was applied.

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