EFFECT OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS ON HEMOGLOBIN LEVELS AMONG PATIENTS WITH ADVANCED CHRONIC KIDNEY DISEASE: A RANDOMIZED CONTROL TRIAL

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Abstract

Background: Anemia commonly occurs among patients with advanced stage chronic kidney disease (CKD) and has been associated with poor clinical outcomes. The role of angiotensin converting enzyme (ACE) inhibitors in aggravating the anemia of patients with CKD is controversial.

Objective: The study aimed to evaluate the effect of ACE inhibitors on hemoglobin levels among patients with advanced CKD.

Methods: Twenty-two patients with CKD stages IV or V and presenting stable hemoglobin levels over 12 weeks were randomly assigned either to receive enalapril (N=10) or amlodipine (N=12) among those whose blood pressure was controlled with antihypertensives other than ACE inhibitors. Hemoglobin levels were monitored at 8 and 16 weeks after treatment.

Results: Clinical characteristics were similar at baseline between the enalapril- and amlodipine-treated groups, and no difference was observed in blood pressure control during follow-up. Enalapril exhibited no significant change in hemoglobin levels from 11.1 g/dL (the interquartile range or IQR 11.1 to 11.5) at baseline to 11.4 g/dL (IQR 10 to 12) at 8 weeks and 10.7 g/dL (IQR 9.9 to 11.8) at 16 weeks of treatment. Hemoglobin levels during the 16-week follow-up declined on average by -0.3 g/dL (IQR -0.9 to 0.4) per 16 weeks in the enalapril group and by -0.1 g/dL (IQR-0.7 to 0.4) per 16 weeks in the amlodipine group (*p*=0.868).

Conclusion: Administration of ACE inhibitors on blood pressure control was not associated with declining hemoglobin levels among patients with advanced CKD. Additional studies are necessary to confirm this result.

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Introduction

Anemia is a common complication of chronic kidney disease (CKD) and is associated with reduced functional status and quality of life, left ventricular dysfunction, congestive heart failure and adverse clinical outcomes.[1, 2] Early identification and treatment of anemia may improve cardiovascular morbidity and mortality. Resistance to recombinant human erythropoietin (EPO) therapy among patients with CKD involves multifactorial etiologies including erythropoietin insufficiency, iron deficiency, inadequate dialysis, bone marrow disease, hemolysis, secondary hyperparathyroidism and use of renin angiotensin aldosterone system (RAAS) inhibitors.[3]

Anemia has been reported as a side-effect of RAAS inhibitors among healthy subjects and patients with essential hypertension, congestive heart failure and renal transplant recipients.[4-8] Additionally, angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) have been linked to reducing response to EPO administration and developing resistant anemia in dialysis.[9-12] Its pathogenesis is multifactorial and may include inhibiting endogenous EPO production, producing an erythropoiesis-inhibiting protein and inhibiting angiotensin II mediated stimulation of erythrocyte precursors.[13,14] Also, data is limited regarding evaluating the effect of ACEI on renal anemia patients with late stage CKD.[5,16] Consequently, no definitive conclusion has been reached concerning the role of ACEI in treating anemia especially among patients with advanced stage CKD. The present study was designed to test the hypothesis regarding administering enalapril to decrease hemoglobin and hematocrit levels among patients with advanced CKD compared with other standard antihypertensive agents.

Methods

This 16-week prospective randomized single blind study was conducted among patients with CKD stages IV to V at the outpatient clinic, Phramongkutklao Hospital. The study was approved by the Institutional Review Board of Phramongkutklao Hospital. Recruitment began August 2014 and was completed January 2015.

Subjects

The inclusion criteria of the study comprised age 18 years or older, CKD stages IV or V and more than 12 weeks with a hemoglobin concentration <12 g/dL among females and <13 g/dL among males. All subjects received stable treatment with antihypertensive agents, lipid lowering agents and metabolic controls for at least 12 weeks and received no treatment with RAAS inhibitors or recombinant human EPO therapy within 12 weeks before starting the study.

Patients with other causes of renal anemia were excluded from the study, i.e., vitamin deficiency, iron deficiency, chronic blood loss, hemolysis or bone marrow disease, hyperkalemia, active malignancy, severe heart, lung or liver disease, stroke, chronic infection, pregnancy, any immuno-logical or inflammatory disorders and known history of enalapril hypersensitivity. All patients provided informed written consent and were questioned to assure that dietary intake and daily lifestyle did not change during follow-up.

Intervention

Eligible patients were randomly assigned to two groups. One group ingested enalapril (N=10), 5 to 20 mg orally daily keeping blood pressure <140/90 mmHg for 16 weeks. The other group ingested amlodipine (N=12), in a similar manner. When maximal doses (20 mg/day for enalapril or 20 mg/day for amlodipine) of initial medications were reached, beta or alpha blocker was added to control high blood pressure more adequately. Adherence was monitored by pill count during each visit.

Clinical and Laboratory Monitoring

Medical history and physical examination were performed for each subject at the outpatient clinic. Casual systolic and diastolic BP were measured using a standard mercury sphygmomanometer applied on the same arm after a 10-minute rest in a sitting position.

After an 8-hour overnight fast, all patients underwent routine laboratory tests including assays for plasma levels of hematocrit, hemoglobin, potassium, creatinine and estimated glomerular filtration rate (GFR) using the 2009 CKD-EPI creatinine equation and staging according to, "The Kidney Disease: Improving Global Outcomes (KDIGO) 2012" at baseline and at the end of the study.

Adverse events that were or were not considered to be related to enalapril treatment were monitored every four weeks.

The patients were questioned in a systematic way about their experiences concerning any adverse events during the previous four weeks. Patients also underwent blood drawing for safety tests including complete blood count and liver function tests. For serious adverse events, enalapril therapy was discontinued at once and the study was terminated.

Statistical Analysis

Measured values of the results were expressed in median with interquartile range (IQR) and percentage. Wilcoxon signed ranks test was used to compare the change of parameters within group at baseline, 8 weeks and 16 weeks. Parameters were compared between groups at baseline, 8 weeks and 16 weeks using the Chi-square, Mann-Whitney and Fischer's exact tests. Statistical analyses were performed using SPSS, Version 15, for Windows (SPSS Inc, Chicago,

IL, USA). A $p < 0.05$ was considered statistically significant.

Results

A total of 42 patients with CKD stages IV to V were screened for possible study enrollment. Twenty-two patients were eligible according to the entry criteria and received enalapril or amlodipine treatment. All patients were 100% adherent to the medication prescription based on pill count and average enalapril dose was 20 mg/day. Mean age was 70.2 years (IQR 61.5-76.2) and mean estimated GFR was 12.4 mL/min/1.73 m^2 (IQR 7.3-24.7). Underlying diseases included hypertension (95%), dyslipidemia (59%), type 2 diabetes (54.5%) and coronary heart disease (22.7%). Characteristics of the patients are shown in **Table 1**. No significant differences were found in age, sex, comorbid diseases, renal function, hemoglobin, hematocrit and iron status.

Table 1. Characteristics of the study population

Variables	Amlodipine (N=12)	Enalapril (N=10)	p-value
Age (yrs)	69.5 (59 to 75.5)	71 (62 to 78)	0.716
Male (%)	5 (41.7%)	7 (70%)	0.231
Smoking (%)	4 (33%)	4 (40%)	1.000
Alcoholic drinking (%)	6 (50%)	4 (40%)	0.691
Underlying disease			
Hypertension	12 (100%)	9 (90%)	1.000
Dyslipidemia	10 (83.3%)	3 (30%)	0.624
Type 2 diabetes	7 (58.3%)	5 (50%)	0.375
Coronary heart disease	2 (16.7%)	3 (30%)	0.455
Serum creatinine (mg/dL)	3.46 (3.5 to 7.0)	3.55 (2.3 to 6.9)	0.262
Glomerular filtration rate (mL/min/1.73	8.7 (6.4 to 15.1)	15.5 (7.6 to 26.3)	0.114
Hemoglobin (g/dL)	10.4 (9.8 to 12.5)	11.1 (11.0 to 11.5)	0.164
Hematocrit (%)	31.6 (29.2 to 37.6)	34.0 (31.4 to 34.5)	0.339
Ferritin (ng/mL)	605.6 (177.2 to 792)	212 (129 to 383.8)	0.147
Transferrin saturation (%)	31.6 (29.9 to 37.4)	39.9 (37.3 to 42.6)	0.099

Data presented as median with IQR

Hematocrit and Hemoglobin Changes after Treatment

Baseline median hematocrit was 32.3% (IQR 29.7 to 35.9) and median hemoglobin was 10.6 g/dL (IQR 9.9 to 11.6). Enalapril showed no significant change in hemoglobin levels from 11.1 g/dL (IQR 11.1 to 11.5) at baseline to 11.4 g/dL (IQR 10 to 12) at 8 weeks and 10.7 g/dL (IQR 9.9 to 11.8) at 16 weeks of treatment (**Figure 1**). Hemoglobin levels during the 16-week follow-up declined on average by -0.3 g/dL (IQR -0.9 to 0.4) per 16 weeks in the enalapril group and by -0.1 (IQR-0.7 to 0.4) per 16 weeks in the amlodipine group ($p=0.868$), but did not reach statistical significance. Moreover, no significant difference was found in median changes in hematocrit and hemoglobin at 8 and 16 weeks between enalapril and amlodipine groups (**Table 2**).
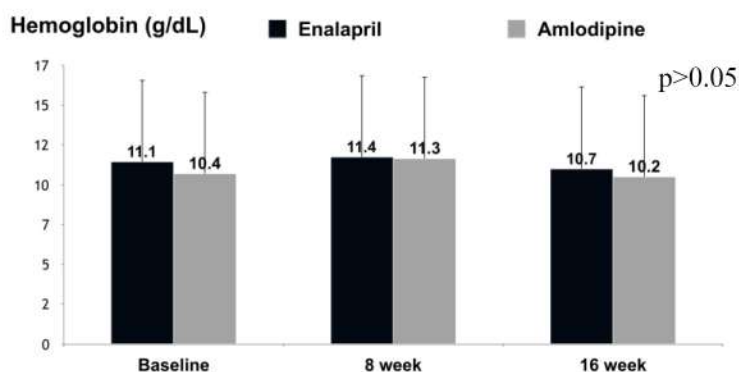

Fig 1. Median levels of hemoglobin after treatment with enalapril and amlodipine. No significant differences were found within and between groups regarding hemoglobin levels any time point ($p > 0.05$).

Table 2. Median changes of hematocrit and hemoglobin after 8 and 16 weeks of treatment

Median changes	Amlodipine (N=12)	Enalapril (N=10)	p-value
Median changes at 8 weeks			
Hematocrit (%)	0.6 (-0.5 to 2.4)	-0.2 (-3.0 to 1.8)	0.356
Hemoglobin (g/dL)	0.1 (-0.2 to 0.6)	-0.2 (-0.9 to 0.5)	0.305
Median changes at 16 weeks			
Hematocrit (%)	-1.1 (-2.5 to 1.1)	-1.3 (-3.1 to 0.3)	0.509
Hemoglobin (g/dL)	-0.1 (-0.7 to 0.4)	-0.3 (-0.9 to 0.4)	0.868

Data presented as median with IQR

Safety Profiles

During the 16-week study period, one of the patients withdrew prematurely because of developing hyperkalemia after initiating enalapril treatment and hyperkalemia subsided upon drug withdrawal. No serious complications were observed and no patient received transfusion during the study.

Discussion

The present study constituted a prospective clinical trial of enalapril treatment concerning anemia status among patients with advanced CKD. Among patients with CKD stages IV to V, compared with baseline, the standard dose enalapril treatment presented a decreasing trend regarding hemoglobin and hematocrit, but without statistical significance. Thus, these findings indicated that antihypertensive treatment using ACEI for 16 weeks did not directly affect anemic status among patients with late stage CKD.

Our results did not demonstrate significant changes in hemoglobin after 16 weeks of enalapril treatment. In contrast, related retrospective and prospective studies have demonstrated that administering RAAS inhibitors lowered hemoglobin levels among patients with CKD undergoing dialysis., However, most reports focused on patients undergoing dialysis concerning recombinant human EPO therapy with high dose RAAS inhibitors or renal transplant recipients.[8-15] However, our study included patients with advanced CKD without dialysis and EPO treatment. Additionally, a large cohort study from Japan indicated that ACEI had no effect on recombinant human EPO therapy treatment concerning anemia among patients undergoing hemodialysis treated with a relatively low dose of ACEI and low-dose recombinant EPO.[17] Furthermore, a prospective, crossover study concerning ACEI treatment for four months among patients undergoing hemodialysis demonstrated that ACEI did not contribute to recombinant human EPO resistance among patients undergoing hemodialysis.[18] Therefore, the negative role of RAAS inhibitors may become more apparent only among dialysis patients receiving exogenous low dose recombinant human EPO treatment and high dose RAAS inhibitors.

Although our results did not demonstrate significant changes in hemoglobin after 16 weeks of treatment, administering enalapril tended to lower hemoglobin levels among patients with advanced stage CKD. Recently, a systemic review and meta-analysis was conducted in seven studies with 29,061 patients clearly indicating an association between anemia and the use of RAAS inhibitors.[19] The negative effect of ACEI on erythrocyte production may imply that ACE inhibitors alter the control of erythropoiesis with reduced sensitivity to EPO and directly inhibit erythropoiesis in vitro.[20,21] Moreover, ACEI also increased the plasma N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) levels at high levels that inhibited erythropoiesis and caused EPO resistance and renal function, essential to maintain low plasma AcSDKP levels.[14, 22, 23] Plasma AcSDKP concentration depended on residual renal function and dose of ACEI used. Thus, the negative results in our study stemmed from using an average dose of enalapril at 20 mg/day among patients with GFR at 12.4 mL/min/1.73 m^2.

This study had several limitations. First, the present study included a relatively small number of patients, but the data were all registered and analyzed in comparison with the control group for 16 weeks of treatment, and factors affecting erythropoiesis other than enalapril were excluded before and during the study. Secondly, short term studies should not imply that enalapril is without long term adverse effects on renal anemia because related studies have documented that patients treated with enalapril needed a higher dose of recombinant human EPO therapy than the control group over the one-year study period. Thirdly, we included major patients with mild anemia with an average hemoglobin level of 10.6 g/dL and without recombinant human EPO therapy, so any negative effects of enalapril on erythropoiesis may have not been detected.

Conclusion

In conclusion, our study did not demonstrate an association between anemia and the use of ACEI among patients with late stage CKD. The effect of ACEI on hemoglobin among patients with CKD should be further assessed using a larger number of patients with a high dose of RAAS inhibitors over a longer treatment period.

Acknowledgements

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