Original Research Article

Effect of angiotensin-converting enzyme inhibitors on response to erythropoietin in chronic renal failure patients

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Abstract

Background: Anaemia is very common in patients with chronic kidney disease. The primary cause of anaemia in patients with CKD is insufficient production of erythropoietin (EPO) by the diseased kidneys. A number of studies have reported that ACE inhibitors antagonized the effects of rHuEPO on the treatment of anaemia in haemodialysis patients. **Aim:** To investigate the efficacy erythropoietin therapy in CRF patients taking ACE inhibitors by evaluating hematocrit values. **Material and Methods:** This study was a prospective and comparative study included 60 chronic renal failure patients undergoing haemodialysis. The study population was divided into three equal groups as follows: Group I – patients were assigned to take recombinant human Erythropoietin (rHuEPO) along with antihypertensive agents other than ACE inhibitors. Group II- patients were assigned to take recombinant human Erythropoietin (rHuEPO) along with ACE inhibitors. Group III- patients were assigned to take ACE inhibitors alone. **Results:** The baseline hematocrit of Group I in the first month was 26.97±0.293%, which increased to 29.36±0.259% over the sixth month. The baseline hematocrit of Group II in the first month was 26.85±0.310%, which increased to 29.26±0.272% over the sixth month. The baseline hematocrit of Group III in the first month was 27.01±0.233%, which showed no significant increase to 26.77±0.237% over the sixth month. **Conclusion:** ACE inhibitors have no effect on the rHuEPO treatment in haemodialysis patients in our analysis. This lack of effect may be due to the relatively low dose of ACE inhibitors and a constant dose of rHuEPO used.

Key Word: Chronic renal failure, anaemia, erythropoietin therapy, ACE inhibitors, haematocrit value

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INTRODUCTION

Kidney disease, some acute but mostly chronic remains a highly prevalent, disabling illness that is associated with a significant social and economic burden. Persons with CKD have significantly higher rates of morbidity, mortality, hospitalizations and healthcare utilization. Anaemia is very common in patients with chronic kidney disease. The kidneys secrete 90% of the endogenous hormone erythropoietin, a hormone necessary for erythropoiesis, declining kidney function can lead to erythropoietin deficiency and anaemia.[1] The primary cause of anaemia in patients with CKD is insufficient production of erythropoietin (EPO) by the diseased kidneys. The prevalence of anaemia in stage 3 chronic kidney disease (i.e., a GFR of 30 to 59 ml/ minute/1.73 m²) was 5.2%, rising to 44.1% in stage 4, and becoming almost universal in stage.[5] Hypertension is commonly treated with antihypertensive agents; like angiotensin converting enzyme (ACE) inhibitors. Drugs such as enalapril (ACE inhibitor) are reno-protective in action. Angiotensin-converting enzyme inhibitors are often the drugs of choice to treat the hypertension. A number of

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studies have reported that ACE inhibitors antagonized the effects of rHuEPO on the treatment of anaemia in haemodialysis patients.[2-4] While a number of possible mechanisms have been identified, there is no consensus. Several studies have been conducted worldwide on the effects of ACE inhibitors on rHuEPO induced erythropoiesis in CRF patients but the reports are contradictory.[5]The present study was therefore aimed at investigating the efficacy erythropoietin therapy in CRF patients taking ACE inhibitors by evaluating hematocrit values.

MATERIAL AND METHODS

This study was carried out in the Department of Nephrology of a tertiary care hospital with the approval of Ethics committee and with the patient informed consent. Patients were selected after making the clinical diagnosis of chronic renal failure. The patients were selected then in accordance with the inclusion and exclusion criteria named below.

Inclusion criteria

- Patients diagnosed to have chronic renal failure on haemodialysis
- Must be able to give voluntary written consent
- Patients who developed a renal disease requiring treatment of their anaemia by subcutaneous EPO.
- Patients of both sex within the age group of 18 to 65 years
- Haemoglobin more than 8 mg/dl

Exclusion criteria

- Haemoglobin less than 8 mg/dl
- Acute Renal Failure
- Severe co-morbidities like congestive cardiac failure, malignancy, infection, severe hyperthyroidism, severe chronic inflammation, sepsis and bed sores.
- Known bleeding or coagulation disorder.
- History of allergic reactions or drug or alcohol abuse
- Positive test results for HIV and AIDS complex, HCV, HbsAg and Syphilis.
- Patient received blood transfusion during the 6 month period
- Any of the following variables -sex, age, body weight, and history of dialysis, pre-treatment hematocrit, rHuEPO dose, serum iron concentration, or classification of underlying diseases-was not available.
- Patients who underwent renal transplantation.

Study design: This study was a prospective and comparative study carried out for a period of six months in 60 chronic renal failure patients undergoing haemodialysis. The duration of study was 6 months.

The study population was divided into three equal groups as follows:

- Group I – In this group, 20 chronic renal failure patients were assigned to take recombinant human Erythropoietin (rHuEPO) along with antihypertensive agents other than ACE inhibitors.
- Group II- In this group, 20 chronic renal failure patients were assigned to take recombinant human Erythropoietin (rHuEPO) along with ACE inhibitors.
- Group III- In this group, 20 chronic renal failure patients were assigned to take ACE inhibitors alone.

Recombinant human Erythropoietin (rHuEPO) was given subcutaneously. Dosage of erythropoietin maintained throughout the study was 100 mg/kg/per week to maintain the Hb >8mg/dl. The antihypertensive agent other than ACE inhibitor used in group I was nifedipine, a calcium channel blocker. Dosage of nifedipine was 5-10 mg/day to maintain blood pressure within 140/90 mmhg. The ACE inhibitor used in groups II and III was enalapril maleate. Dosage of the ACE inhibitor was 5-10 mg/day to maintain blood pressure within 140/90 mm Hg. If the Hb level came below 8 g/dl then the patient was withdrawn from the study and appropriate iron infusion measures were carried out according to the clinician's opinion. If the blood pressure level goes beyond 140/90 mm Hg then the patient should be withdrawn from the study and additional antihypertensive agents were given according to clinician's opinion.

Statistical analysis: The results were analyzed separately for each group and comparative study was carried out between groups. Statistical analysis was done using mean± SEM, and student t-test. Probability $p<0.05$ was considered a statistically significant difference using the Statistical Package for Social Sciences (SPSS) version 15.

RESULTS

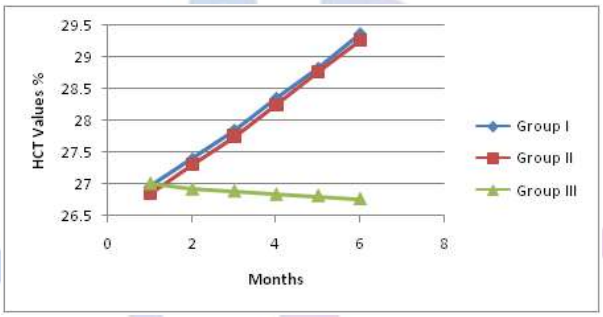
From the original group of 60 patients entered in this study, 20 (33.3%) patients were assigned to group I (recombinant human Erythropoietin (rHuEPO) along with antihypertensive agents other than ACE inhibitors), 20 (33.3%) patients were assigned to group II ((recombinant human Erythropoietin (rHuEPO) along with ACE inhibitors) and rest of the 20 (33.3%) patients were assigned to group III (ACE inhibitors alone). Out of the 20 patients assigned to group III, two patients were withdrawn in the fifth month due fall in haemoglobin level below 8mg/dl, one patient was withdrawn during the sixth month due to fall in haemoglobin level below 8mg/dl. The baseline hematocrit of Group I in the first month was 26.97±0.293%, which increased to

27.40±0.290% over the second month, 27.85±0.299% over the third month, 28.35±0.281% over the fourth month, 28.82±0.276% over the fifth month, and 29.36±0.259% over the sixth month. The baseline hematocrit of Group II in the first month was 26.85±0.310 %, which increased to 27.31±0.313 % over the second month, 27.75±0.317 % over the third month, 28.24±0.288% over the fourth month, 28.77±0.277% over the fifth month, and 29.26±0.272% over the sixth month. The baseline hematocrit of Group III in the first month was 27.01±0.233 %, which showed no significant increase to 26.92±0.224% over the second month, 26.89±0.229 % over the third month, 26.84±0.237% over the fourth month, 26.82±0.233% over the fifth month, and 26.77±0.237% over the sixth month.

Table 1: Hematocrit values in all groups over six months

Months	Hematocrit value		
	Group I (Mean±SD)	Group II (Mean±SD)	Group III (Mean±SD)
1	26.97±0.293	26.85±0.310	27.01±0.233
2	27.40±0.290	27.31±0.313	26.92±0.224
3	27.85±0.299	27.75±0.317	26.89±0.229
4	28.35±0.281	28.24±0.288	26.84±0.237
5	28.82±0.276	28.77±0.277	26.82±0.233
6	29.36±0.259	29.26±0.272	26.77±0.237

Group I and Group II patients who received rHuEPO show a rise in hematocrit values indicating the efficacy of erythropoietin in treating anaemia of chronic kidney disease. Group III patients who received only low dose ACE inhibitors show no significant change in mean hematocrit over six months.



Graph 1: Comparison in mean hematocrit values between groups over six months

A comparison of hematocrit values between group I and group II, was not statistically significant, p = 0.814, 95% CI, 0.397 to 0.314%. This indicates that ACE inhibitors such as enalapril maleate does not exacerbate anaemia when given along with constant dose rHuEPO and hence does not impair erythropoiesis in patients with CKD undergoing haemodialysis.

Table 2: Comparison of hematocrit values between group I and group II

Groups	N	Difference in Hct (t value)	p value	95% confidence interval
rHuEPO along with anti-hypertensive agents other than ACE inhibitors i.e., nifedipine	20	-0.237	0.814	0.03974 to 0.03140
rHuEPO along with ACE inhibitors	20			

A comparison of hematocrit values between group I and group III, was statistically significant, p<0.05, 95% CI, 0.407 to 0.409%. This comparison shows that rHuEPO has a beneficial effect in treating anaemia of chronic kidney disease, as there is improvement in the hematocrit values.

Table3: Comparison of hematocrit values between group I and group III

Groups	N	Difference in Hct (t value)	p value	95% confidence interval
rHuEPO along with anti-hypertensive agents other than ACE inhibitors	20	28.305	0	0.40708 to 0.40998
ACE inhibitors alone	17			

A comparison of hematocrit values between group II and group III, was statistically significant, p<0.05, 95% CI, 0.414 to 0.470%. This indicates that there is significant improvement in hematocrit values when CKD patients on haemodialysis are treated with constant dose rHuEPO. The above results suggest that ACE inhibitors have no effect on the rHuEPO treatment for anaemia in haemodialysis patients who were treated with ACE and constant-dose rHuEPO. This indicates that ACE inhibitors such as enalapril maleate do not exacerbate anaemia when given along with constant dose rHuEPO.

Table 4: Comparison of hematocrit values between group II and group III

Groups	N	Difference in Hct (t value)	p value	95% confidence interval
rHuEPO along with ACE inhibitors	20	32	0	0.41467 to 0.47072
ACE inhibitors alone	17			

DISCUSSION

Angiotensin converting enzyme inhibitors that are routinely prescribed to CRF patients for the treatment of hypertension, left ventricular dysfunction and diabetic nephropathy.[6]Recombinant human erythropoietin (rHuEPO) has been introduced and is currently used throughout the world to treat patients with anaemia. While many investigations have confirmed the efficacy and safety of rHuEPO treatment for renal anaemia, there is concern about the concurrent use of angiotensin-converting enzyme (ACE) inhibitors on the effectiveness of rHuEPO treatment for anaemia. The first report of an interaction between ACE inhibitors and EPO was presented by Walter *et al.*[7]Since then several studies have been conducted worldwide to examine the relationship between concomitant use of rHuEPO and ACE inhibitors to treat anaemia and hypertension but the results are conflicting. The focus of the present study was to compare the effect of ACE inhibitors and other anti-hypertensive agents on erythropoietin therapy in CRF patients. In our analysis, in group I, the erythropoietin along with antihypertensive agents other than ACE inhibitors group, the antihypertensive agent used was nifedipine. In this group, nifedipine is used as it does not interact with recombinant human erythropoietin. The use of nifedipine to treat EPO therapy-related hypertension did not worsen anaemia of chronic kidney disease when compared to the control.[8]Moreover, the dose of rHuEPO required to treat anaemia in CKD remained constant, suggesting that nifedipine does not impair erythropoiesis Nifedipine had an independent effect on blood pressure control in hypertensive patients treated with rHuEPO.[3] Sixty patients (group I (n=20); group II (n=20); group III (n=17) were available for analysis after exclusion for a variety of factors. There was no difference between the two groups in terms of baseline characteristics, number of blood transfusions or hospital days, or other laboratory parameters. There was no statistically significant difference in average hematocrit between groups I and II (p=o.814). These results suggest that ACE inhibitors do not significantly induce more severe anaemia or alter rHuEPO response in chronic haemodialysis patients probably due to the low doses of Enalapril used in this study. The dose of ACE inhibitors used in this analysis was considered relatively low compared to other studies.[3,4,9-11]Charytan *et al*[12] also used a low dose ACE inhibitor (enalapril maleate, 11±10.7 mg/day) compared with Albiter *et al* study,[3] and concluded that ACE inhibitors did not affect the rHuEPO dose needed to treatment. The dose of rHuEPO administered in our analysis was 100U/kg. Our results differ from earlier communications reporting that ACE inhibitors reduced the effectiveness of rHuEPO treatments in renal anaemia. Albitar *et al* showed that most patients received a high dose of enalapril (20 mg/day) in their study.[3] In their study, the targeted hematocrit value was not high (about 30%), while the dose of ACE inhibitor used by patients was high. In other words, these studies showed that high-dose ACE inhibitors exacerbated anaemia.Cruz *et al* conducted two studies,[10] a retrospective analysis and a prospective study based on their earlier retrospective study. Although an analytical weakness was noted in the prospective study, both studies reached conclusions similar to our findings. However, unlike our survey, those authors used high doses of ACE inhibitors (lisinopril ~ 24 mg/day and enalapril maleate ~20 mg/day). At the same time, they reported a high target hematocrit value (~33%). These results suggest that any effect of high-dose ACE inhibitors can be overcome by high-dose rHuEPO. Angiotensin-converting enzyme inhibitors diminished the circulating angiotensin II levels, leading to reductions in both endogenous erythropoietin levels and erythropoiesis. ACE inhibitors also increased the Ac-SDKP levels, thus exacerbating the anaemia.[13,14] [Rousseau *et al* 1999; Lenfant *et al* 1989]. However, exogenous rHuEPO could overcome any effects of ACE inhibitors on haematopoiesis. These findings taken together allow us to speculate that the inhibitory effect of ACE inhibitors may be apparent only when high-dose ACE inhibitors and low-dose rHuEPO (or a low target hematocrit value) are administered together to a haemodialysis patient.

CONCLUSION

From this study, we conclude that ACE inhibitors have no effect on the rHuEPO treatment in haemodialysis patients in our analysis. This lack of effect may be due to the relatively low dose of ACE inhibitors and a constant dose of rHuEPO used. Our analysis could not identify the doses of ACE inhibitors and rHuEPO that are critically important for the treatment of renal anaemia. Further investigations with ACE inhibitors and rHuEPO should be examined in a large cohort of patients to identify their interactions.

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