Original Research Article

Study of erythropoietin efficacy by recombinant erythropoietin therapy along with ace inhibitors and ace inhibitors alone in chronic renal failure

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Abstract

Background: Anaemia and hypertension are the most common complications of CKD. To counter anaemia, patients with CRF are regularly treated with erythropoietin. There is concern about the concurrent use of angiotensin-converting enzyme (ACE) inhibitors on the effectiveness of rHuEPO treatment for anaemia. **Aim:** To evaluate the erythropoietin efficacy by recombinant erythropoietin therapy along with ACE inhibitors and ACE inhibitors alone in chronic renal failure. **Material and Methods**: The study population was divided into two groups. The groups were as follows: Group I- 20 chronic renal failure patients are assigned to take recombinant human Erythropoietin (rHuEPO) along with ACE inhibitors; Group II- 20 chronic renal failure patients are assigned to take ACE inhibitors alone. **Results:** The baseline hematocrit of Group I 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 II in the first month was 27.01±0.233%, which showed no significant increase to 26.77±0.237% over the sixth month. **Conclusion:** From this study it can be concluded that ACE inhibitors have no effect on 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 in this study.

Key Word: Chronic kidney disease, anaemia, hypertension, ACE inhibitors, Erythropoietin

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INTRODUCTION

Anaemia is very common in patients with chronic kidney disease and probably causes many of its symptoms. The kidneys secrete 90% of the endogenous hormone erythropoietin, a hormone necessary for erythropoiesis. Anaemia mainly results due to lack of endogenous erythropoietin (EPO) production from failing kidneys. To counter anaemia, patients with CRF are regularly treated with erythropoietin, iron and other haematinics.[1] Hypertension is one of the most common complications of CKD. It usually develops early during the course of CKD and is associated with adverse outcomes, including the development of ventricular hypertrophy and a more rapid loss of renal function. 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.[2] The present study was conducted to evaluate the erythropoietin efficacy by recombinant erythropoietin therapy along with ACE inhibitors and ACE inhibitors alone in chronic renal failure.

MATERIAL AND METHODS

This prospective study was carried out in 60 chronic renal failure patients undergoing haemodialysis the Department

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of Nephrology in a tertiary care hospital in Chennai for a period of six months. The study was started after the approval of Institutional Ethics Committee and with the patient informed consent.

Study population: The patients enrolled were residents of the urban area of Chennai and also from the surrounding semi-urban and rural areas. 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 of both sex within the age group of 18 to 65 years
- 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.
- Haemoglobin more than 8 g/dl.

Exclusion criteria

- Haemoglobin less than 8 g/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.

Patient groups

The study population was divided into two groups. The groups were as follows:

- Group I- In this group, 20 chronic renal failure patients are assigned to take recombinant human Erythropoietin (rHuEPO) along with ACE inhibitors
- Group II- In this group, 20 chronic renal failure patients are 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 ACE inhibitor used in groups I and II 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 study was conducted for a period of six months. Every month the hematocrit values of the patient were evaluated. 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

In this study, 20 (50%) patients were assigned to group I(recombinant human Erythropoietin along with ACE inhibitors) and rest of the 20 (50%) patients were assigned to group II (ACE inhibitors alone). Out of the 20 patients assigned to group II, two patients were withdrawn in the fifth month due fall in haemoglobin level below 8 g/dl, one patient was withdrawn during the sixth month due to fall in haemoglobin level below 8 g/dl. The baseline hematocrit of Group I 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.

Table 1: Mean monthly Hematocrit values of Group I

Months	HCT Values (%)
1	26.85±0.310
2	27.31±0.313
3	27.75±0.317
4	28.24±0.288
5	28.77±0.277
6	29.26±0.272

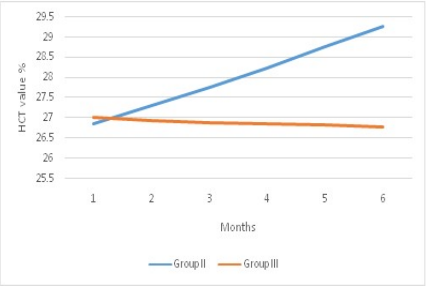
The baseline hematocrit of Group II in the first month was 27.01±0.233%, which showed no significant increase to 26.92±0.224% over the second month, 26.89±0.229% over the third month, 26.84±0.237% over the fourth month, 26.82±0.233% over the fifth month, and 26.77±0.237% over the sixth month.

Table 2: Mean monthly Hematocrit values of Group II

Months	HCT Values (%)
1	27.01±0.233
2	26.92±0.224

3	26.89±0.229
4	26.84±0.237
5	26.82±0.233
6	26.77±0.237

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 II 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 6 months

Table 3: Comparison of hematocrit values between group I and group II

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

A comparison of hematocrit values between group I and group II, was statistically significant, $p<0.05$, 95% CI, 0.414 to 0.470%. This indicates that there was significant improvement in hematocrit values when CKD patients on haemodialysis were 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.

DISCUSSION

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. Angiotensin-converting enzyme (ACE) inhibitor are widely used in renal failure patients in the treatment of hypertension.[1] Its efficacy in these conditions is well established, and generally these drugs are well tolerated, with a low incidence of side effects.[3] In recent years, much interest has focused on the potential for ACE inhibitors to suppress erythropoiesis, and thereby exacerbate anaemia.[4,5] Moreover, much controversy has also been generated over whether ACE inhibitors affect the efficacy of erythropoietin (rHuEPO) in chronic renal failure patients. Some studies seem to suggest that ACE inhibitors may affect erythropoiesis,[6-9] while others have found no effect.[10-12] In group I, the combination therapy group (rHuEPO with concurrent ACE inhibitor treatment) and in group II, i.e., monotherapy group (ACE inhibitor alone), the ACE inhibitor used was enalapril maleate. It is a prodrug which on being hydrolysed by hepatic esterases, is transformed into an active form, enalaprilat. In this analysis 20 patients received enalapril maleate between doses of 5 to 10mg/day. The dose of ACE inhibitors used in this analysis was considered relatively low compared to other studies.[3,13-15] Charytan et al[16] 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,[14] 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.[17,18] 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 it can be concluded that ACE inhibitors have no effect on 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 in this study.

Limitations of the study: It is accepted that the present study was conducted on a small number of patients, which warrants further studies to be conducted at a larger scale with a greater number of patients taken from throughout the country to get more meaningful data on CRF patients under these conditions. Nonetheless, our study concludes that CRF patients receiving rHuEPO for anaemia treatment and ACE inhibitors for hypertension face no impairment of erythropoiesis as has been observed by Hayashi *et al.*

REFERENCES

1. Remuzzi G, Rossi EC. Hematological consequences of renal failure. In:Brenner MB, Rector FC, editors. The kidney. Philadelphia:WB Saunders: 1995.
2. Hayashi K, Hasegawa K, Kobayashi S. Effects of angiotensin converting enzyme inhibitors on the treatment of anemia with erythropoietin. Kidney Int 2001; 60: 1910-1916.
3. Albitar S, Genin R, Fen-Chong M, Serveaux M, Bourgeon B. High dose enalapril impairs the response to erythropoietin treatment in hemodialysis patients. Nephrol Dial Transplant 1998; 13: 1206-1210.
4. Naito M, Kawashima A, Akiba T, Takanshi M, Nihei H. Effect of an angiotensin II receptor antagonist and angiotensin converting enzyme inhibitors on burst forming units-erythroid in chronic hemodialysis patients. Am J Nephrol 2003; 23: 287- 293.
5. Grossmann J, Thuram P, Bachmann T, Weller S, Kachel HG, Schoeppe W, *et al.* Mechanism of angiotensin converting enzyme inhibitor related anemia in renal transplant recipients. Kidney Int 1996; 50: 973-978.
6. Danovitch GM, Jamgotchian JN, Eggena PH, Paul W, Barette JD, Wilkinson A, *et al.* Angiotensin converting enzyme inhibition in the treatment of renal transplant erythrocytosis. Clinical experience and observation of mechanism. Transplantation 1995; 60: 132-137.
7. Rivalan J, Morin MP, Joyeux V, Le Pogamp P. Post-transplant erythrocytosis treatment with Losartan. J Am Nephrol 1996; 7:1939.
8. Mrug M, Stopka T, Bruce AJ, Jaroslav FP, Josef TP. Angiotensin II stimulates proliferation of normal early erythroid progenitors. J Clin Invest 2000; 100: 2310-2314.
9. Azizi M, Rousseau A, Ezan E, Guyene TT. Acute angiotensin converting enzyme inhibition increases the plasma levels of natural stem cell regulator N-acetyl-seryl-aspartyl-lysyl-proline. J Clin Invest 1996; 97: 839-844.
10. Danser AH, Saris JJ, Schuijt MP, Vankats JP. Is there a local renin angiotensin system in the heart? Cardiovasc Res 1999; 44: 252-265.
11. Lafayette RA, Mayer G, Park SK, Meyer TW. Angiotensin II receptor blockade limits glomerular injury in rats with reduced renal mass. J Clin Invest 1992; 90: 766-771.
12. Dechow C, Morath C, Peters J, Lehrke I, Waldherr R, Haxsen V, *et al.* Effects of all-trans retinoic acid on renin-angiotensin system in rats with experimental nephritis. Am J Physiol Renal Physiol 2001; 281: F909-F919.
13. Erturk S, Nergizoglu G, Ates K, *et al.* The impact of withdrawing ACE inhibitors on erythropoietin responsiveness and left ventricular hypertrophy in haemodialysis patients. Nephrol Dial Transplant. 1999; 14: 1912–1916.
14. Cruz DN, Perazell MA, Abu-Alfa AK, Mahnensmith RL. Angiotensin-converting enzyme inhibitor therapy in chronic hemodialysis patients: Any evidence of erythropoietin resistance?. Am J Kidney Dis. 1996; 28: 535–540.
15. Abu-Alfa AK, Cruz D, Perazella MA, *et al.* ACE inhibitors do not induce recombinant human erythropoietin resistance in hemodialysis patients. Am J Kidney Dis. 2000; 35: 1076–1082.
16. Charytan C, Goldfarb-Rumyantzev A, Wang YF, *et al.* Effect of angiotensin-converting enzyme inhibitors on response to erythropoietin therapy in chronic dialysis patients. Am J Nephrol. 1998; 18: 498–503.
17. Rousseau A, Michaud A, Chauvet M-T, *et al.* The hemoregulatory peptide N-acetyl-Ser-Asp-Lys-Pro is a natural and specific substrate of the N-terminal active site of human angiotensin-converting enzyme. J Biol Chem. 1995; 270: 3656–3661.
18. Lenfant M, Wdzieczak-Bakala J, Guittet E, *et al.* Inhibitor of hematopoietic pluripotent stem cell proliferation: Purification and determination of its structure. Proc Natl Acad Sci USA. 1989; 86: 779–782.

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