Evaluation of Effect of Statins on Erythropoietin Resistance in Patients of Chronic Kidney Disease on Maintenance Haemodialysis

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Abstract

This study was planned to evaluate the effect of statin on erythropoietin resistance and HsCRP levels in patients of chronic kidney disease on maintenance haemodialysis.

Methods: Thirty adult patients of end stage renal disease with erythropoietin hyporesponsiveness undergoing maintenance hemodialysis were included in the study. Patients were divided randomly into two groups of 15 patients each. Group A were given atorvastatin in a dose of 20 mg once daily for a period of 4 months along with erythropoietin 6000 IU S/C and IV iron 100mg twice weekly after each hemodialysis. Group B was given erythropoietin 6000 IU S/C and IV iron 100 mg twice weekly after each hemodialysis without addition of atorvastatin for 4 months. Hematological, renal parameters, inflammatory parameters such as erythrocyte sedimentation rate, highly sensitive C reactive protein, serum ferritin and erythropoietin resistance index were done at baseline and then two monthly intervals for 4 months.

Results: At the end of study, in group A hemoglobin and haematocrit significantly increased ($p < 0.001$ for both) while HsCRP, ESR and erythropoietin resistance index decreased significantly ($p=0.001$, 0.001 and <0.001 respectively). In group B, the increase in hemoglobin and haematocrit were not statistically significant ($p > 0.05$) similarly fall in HsCRP and ERI were also not significant statistically ($p > 0.05$). The mean rise in hemoglobin between subsequent months was higher in group A as compared to group B which was statically significant.

Conclusion: Statin can be used as an adjuvant to erythropoietin in management of anemia in patients of chronic kidney disease, who show hyporesponsiveness to increased doses of erythropoietin, by its anti-inflammatory properties.

Introduction

Anaemia of end-stage renal disease patients has been effectively treated with erythropoietin. Erythropoietin stimulating agents hyporesponsiveness is one of the major issues in dialysis patients. Improving ESA hyporesponsiveness not only improve patient's quality of life, but also reduce the burden of care cost.[1–2] Factors causing erythropoietin hyporesponsiveness include iron deficiency, infections, inadequate dialysis, chronic blood loss, hyperparathyroidism, aluminum toxicity, malnutrition, vitamin deficiency and others.[3] Patients with end-stage renal disease are prone to inflammation and inflammation is related to erythropoietin-stimulating agent hyporesponsiveness and mortality in this population. C-reactive protein (CRP), an acute phase protein, is the most commonly used marker of inflammation in chronic kidney disease (CKD) patients. CRP predicts mortality in HD patients and high levels of CRP have been associated with resistance to EPO therapy in HD patients, indicating the presence of some microinflamma tion.[4]

Dyslipidemia is prevalent in maintenance haemodialysis patients. Statin therapy has been demonstrated to not only be effective in lowering lipid levels, but also have numerous pleiotropic effects including anti-inflammatory, anti-fibrotic and endothelial function improvement. Study has shown that statin treatment successfully reduced ESA requirements by 25% in MHD patients.[5] They observed its possible mechanisms through anti-inflammatory effects. This study was planned to evaluate the effect of statin therapy in ESA hyporesponsiveness.

Material and Methods

Thirty adult patients [15 patients in group A receiving erythropoietin 6000 IU, IV Iron and Atorvastatin and 15 in group B receiving erythropoietin 6000 IU, IV Iron but without Atorvastatin] of ESRD with erythropoietin hyporesponsiveness undergoing maintenance hemodialysis were included in the study. Patients were randomly divided into two groups (15 in each). In Group A were given Atorvastatin in a dose of 20 mg once daily for a period of 4 months along with erythropoietin 6000 IU S/C and IV Iron 100mg twice weekly after each hemodialysis. Group B was given erythropoietin 6000 IU S/C twice weekly after each hemodialysis and IV iron 100 mg/week without addition of Atorvastatin for 4 months. Hematological and renal investigations, ESR, HsCRP and serum ferritin were done at baseline and then two monthly intervals for 4 months.

Serum ferritin was measured using a two-site sandwich immunoassay based on direct chemiluminometric technology, which uses constant amounts of two anti-ferritin antibodies.[6] Hs-CRP was measured using latex–enhanced immunonephelometric assay. Statistical analysis was performed using SPSS software version – 17.0. For comparison of means of same parameter in two groups unpaired students t test was used and p-values obtained to determine the statistical significance. For comparison of means of same parameter in a single group at two point of time during follow up paired

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Table 1: Comparison of haematological and inflammatory parameters in two groups

Parameters	Group A			Group B			
	Baseline	At 4 Months	P value* (paired)	Baseline	At 4 Months	P value* (paired)	P value** (unpaired)
Hemoglobin (g/dl)	6.36±0.81	8.96±0.55	<0.001	6.50±1.05	7.04±0.79	0.122	<0.001
Hematocrit (%)	19.15±2.40	29.63±3.45	<0.001	19.28±2.24	20.65±2.02	0.086	<0.001
Hs CRP	3.50±1.46	1.26±0.90	0.001	3.23±0.89	3.13±0.65	0.662	<0.001
ESR	44.20±14.29	30.53±5.62	0.001	46.20±13.40	44.8±11.72	0.763	<0.001
S. Ferritin	615.60±261.04	486.13±135.84	0.006	614.00±407.11	599.00±223.69	0.925	0.106
ERI	38.67±11.33	26.81±5.71	<0.001	43.62±12.18	39.67±9.78	0.336	<0.001

*P value between baseline and end of study; data is represented as mean ± SD; **p value between both groups at end of study; data is represented as mean ± SD

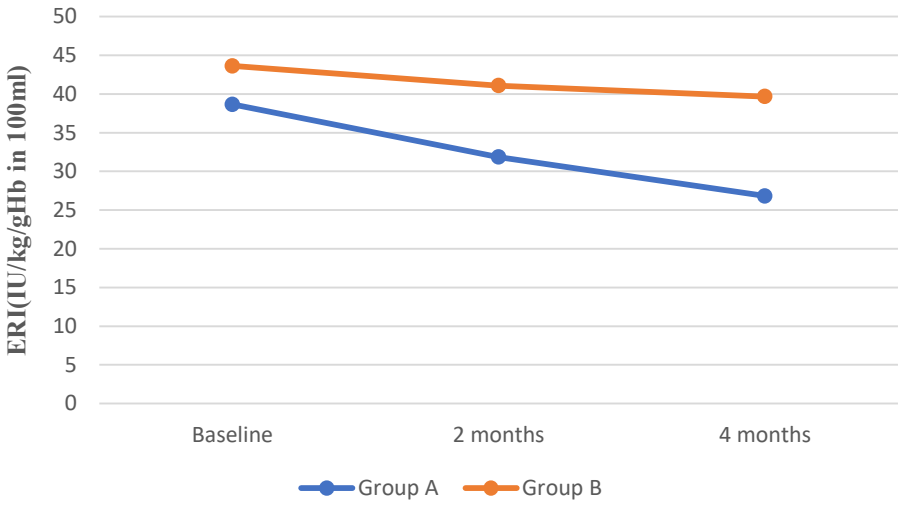

Fig. 1: Comparison of erythropoietin resistance index in both groups during study periods

students t test was used and p-values obtained to determine the statistical significance. For comparison of means of different parameters at 0, 1, 2, and 3 months repeated measures analysis of variance (ANOVA) test was used and p-values obtained to determine the statistical significance. The p values were two tailed and probability level of significant difference was set at <0.05 for both paired and unpaired students t test and ANOVA test.

Results

102 patients of CKD who were undergoing regular maintenance hemodialysis were screened. 46 patients were found to have erythropoietin resistant (inadequate rise in Hb <1g/dl rise in Hb in one month). The dose of erythropoietin was increased to 6000 I.U. S/C twice weekly, and response was seen after two months. 8 patients showed good response to increased dosage of erythropoietin, 6 patients were using statins for ischemic heart disease, two patient developed lower G.I. bleeding due to haemorrhoids so were also excluded. So, final group of 30 patients were labeled as erythropoietin resistant and were included in the study. They are divided into Group A (Statin) and Group B (Nonstatin). Patients were follow up for 4 months and response was seen.

Mean age of study participants were 45.55±14.54 and 49.8±12.79 years in group A and group B, respectively. Hypertension was the most common cause of CKD in both the groups (7 in group A and 9 in group B) followed by diabetic nephropathy which accounted for (5 in group A and 1 in group B patients). The various hematological and renal parameters in group A and group B were comparable at baseline. At the end of study, in group A, Hb significantly increased from 6.36±0.81 to 8.96±0.545 g/dl (P <0.001) and hematocrit increased from 19.15±2.40 to 29.63±3.45% (P <0.001), while ESR, Hs-CRP and ERI decreased significantly from 44.20±14.29 to 30.53±5.62 mm 1st hr (P =0.001), 3.50±1.46 to 1.26±0.90 mg/dl (P = 0.001) and 38.67±11.33 to 26.81±5.73 IU/kg/g Hb in100 ml (P <0.001). In group B, the increase in Hb and haematocrit were not significant statistically (P >0.05). Among inflammatory parameters there was fall in ESR, Hs-CRP, S.ferritin and ERI but not significant statistically (P>0.05). The mean rise in hemoglobin between subsequent months was higher in group A as compared to group B (Table 1). ERI in group A was correlated with baseline hemoglobin and other inflammatory parameters by using Spearman coefficient of correlation and it was observed that ERI showed positive correlation with inflammatory markers HsCRP (r = 0.575) and ESR (r = 271) (Figures 1, 2). Comparison of erythropoietin resistance index in both groups during study periods. ERI was used as an index to evaluate the dose-response effect of EPO therapy. ERI in group A was 38.67±11.33, 31.84±8.18 and 26.81±5.71 at baseline, 2 months and 4 months, respectively and the fall was statistically significant (p <0.001), whereas in group B, the ERI was 43.62±12.18, 41.08±11.01 and 39.67±9.78 at baseline, 2 months and 3 months, respectively and the change was not significant statistically (p >0.05). This suggests that atorvastatin given to group A has decreased EPO resistance probably by its pleiotropic effect and anti-inflammatory properties. Correlation between erythropoietin resistance index and hemoglobin. ERI in group A was correlated with baseline hemoglobin by using Spearman Coefficient of correlation and it was observed that ERI was negatively correlated to hemoglobin (r =-0.691) ERI was strongly correlated with HsCRP (Odds ratio=8.8) showing that HsCRP is a major contributor for erythropoietin resistance (Figure 3). Correlation between erythropoietin resistance index and highly sensitive C reactive protein. ERI in group A was correlated with inflammatory marker Hs CRP by using Spearman coefficient of correlation and it was observed that ERI showed positive correlation with HsCRP (r = 0.575) and was strongly correlated with HsCRP (Odds ratio=8.8) showing that HsCRP is a major contributor for erythropoietin resistance. There was significant fall in serum TG, VLDL and rise in serum HDL levels. The changes in serum sodium, serum potassium, serum calcium, serum proteins, proteinuria and GFR, blood pressure in both the groups were not found to be statistically significant

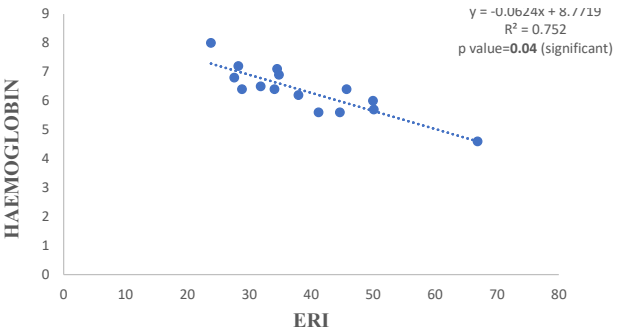

Fig. 2: Correlation between erythropoietin resistance index and hemoglobin

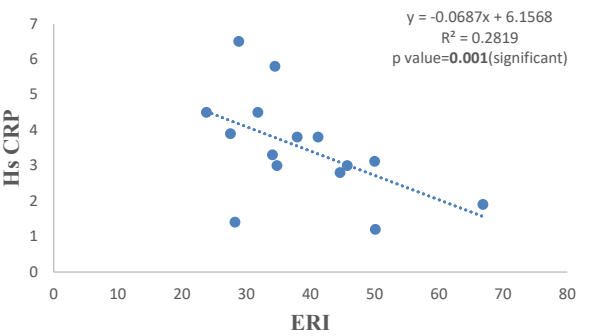

Fig. 3: Correlation between erythropoietin resistance index and highly sensitive C reactive protein

(p>0.05)

Discussion

Anemia develops early in the course of CKD and is nearly universal. It is directly correlated with the degree of impairment of renal function and considered one of the hallmarks of renal disease. The anemia of CKD is characteristically hypoproliferative and normocytic normochromic red cells and is due to decreased production of erythropoietin by the diseased kidneys. It contributes to poor quality of life (QOL) and adverse pathophysiologic consequences both due to effects of decreased oxygen delivery to tissues and to the heart's compensatory mechanism.[7] Erythropoiesis-stimulating agents (ESA) has resulted in substantial health benefits, including improved quality of life, reduced blood transfusion requirements and enhanced exercise capacity. However, 5–10% of patients show hyporesponsiveness and contributes to morbidity, mortality and health-care economic burden. ESA hyporesponsiveness may be due to number of factors and increasing the dosage of EPO and maintaining adequate iron stores, by administering iron parenterally, is the most important measures for reducing the requirements and enhancing the efficacy of ESA. It has also been improved by a number of interventions, including the use of biocompatible membranes, ultrapure dialysate, transplant, nephrectomy, ascorbic acid therapy, vitamin E supplementation, statins and pentoxifylline administration.

Chronic inflammation is a common feature of CKD and is a major cause of morbidity and mortality. In CKD, erythropoiesis is inhibited by several pro-inflammatory cytokines such as interleukin-1, tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ).[8] Studies has shown that high plasma concentrations of C-reactive protein (CRP) have found to be associated with anemia and ESA hypo responsiveness in chronic hemodialysis patients.

Several studies evaluated the effect of 3-hydroxy-3-methylgluatryl coenzyme A reductase (HMG–CoA) reductase inhibitors on inflammatory markers CRP levels, showing significant reductions with statin therapy. Statin therapy attenuates endothelial dysfunction, enhances renal perfusion and reduces abnormal permeability to plasma proteins.[9] Statins exert an antioxidant effect with a mechanism potentially involving downregulation of Nox2 and upregulation of nitric oxide synthase coupling.[10] Statins also cause decreased macrophage expression of soluble intercellular adhesion molecule-1 and lipopolysaccharide-induced secretion of IL-6 and TNF-α by monocytes and macrophages. Statin induced decrements in CRP levels appear to be a class effect as evidenced by several studies. In a retrospective study by sirken et al. found that there was a significant rise of mean hemoglobin with 25% reduction in EPO dose, after initiation of treatment with statins. Studies have proved that EPO hypo responsiveness was significantly reduced along with reduction in inflammatory markers. They also found a trend of decreasing hsCRP levels, but it was statistically insignificant.[12-13] Study done by KOC M et al. also demonstrated high-sensitive C-reactive protein levels were significantly decreased in statin users compared with nonusers. Also, erythropoietin-stimulating agent dose and the erythropoietin response index were lower in statin users compared with statin nonusers.[14]

In this study, we found that use of statin (Group A) for short duration in patients who had EPO hypo responsiveness, there is improvement in haemoglobin and haematocrit while reduction in the high level of inflammatory parameters (HsCRP, ESR, Serum ferritin). In group B, there is slight increase in hemoglobin, haematocrit and fall in levels of inflammatory parameters is not significant, suggestive of persistent EPO hyporesponsiveness. In this study, ERI was used as an index to evaluate the dose-response effect of EPO therapy. In group A, at the end of study fall in ERI was statistically significant, whereas in group B, the fall was not significant statistically. This suggests that statins given to patients has decreased EPO resistance probably by overcoming EPO hyporesponsiveness secondary to its anti-inflammatory property. We tried to exclude all other factors responsible for erythropoietin resistance. In this study rain canal water was used which did not contain aluminum. Infection was treated aggressively as early as possible. Therefore, probable factor which was operative for the decreased hemoglobin in group B was most probably due to chronic inflammatory state which is essentially a basic feature of CKD. There are many preclinical studies on the pleiotropic effect of statins on inflammation. This property of statins may be mediated in part by reduced monocyte expression of proinflammatory cytokines, interleukin-6 and tumor necrosis factor-α.

It can therefore be concluded that statin use is associated with a decrease in inflammation (namely hsCRP) and improved response to ESA treatment. This study suggests that preventing or correcting inflammation by statin use might provide better management

of anemia and a lower mortality in HD patients. A larger prospective, randomized, controlled trial is needed for further support and stronger evidence for this finding.

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