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THE EFFECT OF ERYTHROPOIETIN ON HIGH DENSITY LIPOPROTEIN LEVELS OF KIDNEY DISEASE PATIENTS (STAGE 5)

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ABSTRACT

Chronic kidney disease is a global threat to health in general and for developing countries. Erythropoietin is the treatment of choice in anemia of renal disease. It acts by binding on to the receptors present in the surface of marrow erythroid progenitor cells, colony forming units; thus increasing its proliferation. Decreased HDL level may be a risk factor for cardiovasculardiseases similar in importance to increased LDL level. Thus interventions that increase HDL level are antiatherosclerotic. Erythropoietin acts by improving tissue oxygenation and increases the reverse cholesterol transport processs. Thereby increasing the HDL level. As there are only few studies in Indian literature regarding the effect of erythropoietin on HDL levels in CKD patients (stage 5), the present study is undertaken.

INTRODUCTION

Chronic kidney disease, also called chronic renal insufficiency or progressive kidney disease by some, is defined as a progressive loss of function occurring over several months to years, and is characterized by the gradual replacement of normal kidney architecture with interstitial fibrosis. National Kidney Foundation(NKF) has developed a CKD classification system based on the presence of structural kidney damage and/or functional changes in Glomerular Filtration Rate (GFR) present for a period of 3 months or more.CKD is categorized by the level of kidney function (as defined by GFR) into stages 1 to 5, with each increasing number indicating a more advanced stage of the disease.

Normal kidney function in adults is approximately 120 ml/min/1.73 m2 of GFR. Even though a GFR of >90 ml/min/1.73 m2 is considered normal kidney function, a patient can be diagnosed with CKD if the patient has proteinuria, hematuria, or evidence of structural damage from a kidney biopsy. The symptoms will develop slowly, which includes:

- anorexia
- nausea
- vomiting
- stomatitis
- nocturia
- fatigue
- pruritis
- decreased mental ability
- water retention

The major cause for CKD is diabetic nephropathy followed by hypertensive nephrosclerosis and various primary and secondary glomerulopathies. Metabolic syndrome, in which hypertension and type2 diabetes are present, is a large and growing cause of renal damage.

Anemia is characteristic of moderate to advanced CKD (≥ stage 3). It is a hypoproliferative anemia resulting primarily from deficient erythropoietin (EPO) or a diminished response to it; it tends to be normocytic and normochromic. The primary cause of anemia in CKD patients is a decrease in production of the hormone erythropoietin by the progenitor cells of the kidney, where 90% of production typically occurs. Plasma concentrations of erythropoietin increase exponentially in individuals with normal kidney function as hemoglobin/hematocrit decline (i.e., in response to decreased oxygenation). Iron deficiency is the primary cause of

resistance to therapy with erythropoieticstimulating agents (ESAs; i.e., epoetin alfa or darbepoetin alfa)

The **most common mechanism** of anaemia in CKD are:

- Hypoproliferation due to decreased EPO production

- Other factors include
  - Uremia (in which mild hemolysis is common due to an increase in RBC deformity)
  - Blood loss due to dysfunctional platelets, dialysis, and/or angiodysplasia
  - Secondary hyperparathyroidism

Erythropoeitin at a beginning dose of 50 to 100 units/kg is the treatment of choice in anemia of renal disease.It acts by binding on to the receptors present in the surface of marrow erythoid progenitor cells, colony forming units (CFU-E). Thus increasing its proliferation.

Dyslipidemia may be associated with kidney disease.CKD with or without nephrotic syndrome is frequently accompanied by abnormalities in lipoprotein metabolism. The prevalence of hyperlipidemia appears to increase as kidney function declines. In 85% to 90% of patients with decreased kidney function and proteinuria greater than 3 g/day, elevated plasma total and low-density lipoprotein cholesterol occurs. Approximately 50% of these patients have low levels (<35 mg/dL) of high-density lipoprotein cholesterol,and 60% have triglyceride concentrations greater than 200 mg/dL.Lipid-lowering agents can decrease the extent of glomerular injuryin patients with hyperlipidemia and kidney disease. Therefore,treatment of lipid abnormalities in patients with CKD mayhave a beneficial effect on slowing the rate of progression of thekidney disease.

REVIEW OF LITERATURE

1 Samar K.M Khalil et al (2016) conducted a study on "Oxidative stress during erythropoietin hypo responsiveness anemia at end stage renal disease: molecular and biochemical studies."

In this study a group of 80 ESRD patients treated with rhEPO was selected. All patients were supported with L-Carnitine and B-complex supplementation after each session of HD. The patients were divided into erythropoietin poor responders and good responders. In order to improve responsiveness to rhEPO therapy oral supplementation with vitamin c was prescribed and monitor before and after HD. The work proved that antioxidant vitamin c supplementation –in lower dosing- may enhance antioxidant defense mechanisms with mitigation of oxidative damages and thus reducing the requirement of high rhEPO dosing.

2 Nobuharu Fujiwara et al (2011) conducted a study on the topic" Renovascular Protective Effects of Erythropoietin in Patients with Chronic Kidney Disease".

The aim of the study was to determine whether EPO affects renovascular and oxidative stress biomarkers in pre-dialysis CKD patients with anemia. Fifteen CKD patients (9 males and 6 females,mean age 63 years) with anemia (mean Hb: 8.1 g/dL) were treated with recombinant human EPO; 12,000 U administered subcutaneously once every 2 weeks. Various parameters were measured before and 6 months after treatment. These included serum hemoglobin (Hb), creatinine, estimated glomerular filtration rate (eGFR), proteinuria, urinary liver-type fatty acid binding protein (L-FABP - a biomarker of renal injury), urinary 8-hydroxydeoxyguanosine (8-OHdG - a marker of oxidative stress), serum asymmetrical dimethylarginine(ADMA), carotid artery intima-media thickness (IMT) and brachial-ankle pulse wave velocity (baPWV) asvascular markers and plasma brain natriuretic peptide (BNP) levels and left ventricular ejection fraction LVEF) as cardiac function markers and cardio-thoracic ratio (CTR) and inferior vena cava dimension (IVCS) as extra fluid retention markers. After 6 months, serum Hb was significantly increased ($p<0.001$) and urinary levels of protein, LFABP and 8-OHdG, carotid IMT, baPWV, plasma BNP and serum ADMA levels were significantly decreased ($p<0.001$). Serum creatinine, eGFR, LVEF, CTR and IVCS showed little difference throughout the experimental period. These data suggest that recombinant human EPO may ameliorate renal injury, oxidative stress and progression of atherosclerosis in addition to improving anemia in CKD patients.

3 Giovanni F. M. Strippoli (2008) et al conducted a study on the effect of statins in patients with chronic disease.

30144 patients were studied and compared with placebo. Statins significantly reduced total cholesterol, LDL and proteinuria. But the treatment did not improve GFR. Fatal and non fatal cardiovascular events were reduced with the use of statins. The side effect profile was similar to that of placebo. Thus statins significantly reduced lipid concentration and cardiovascular risks in patients with CKD irrespective of the stage of disease.

4 ***SIMON D. ROGER (2004)*** et al conducted a study on the topic Effects of Early and Late Intervention with Epoetin α on Left Ventricular Mass among Patients with Chronic Kidney Disease (Stage3 or 4)

It's a randomized controlled trial performed with 155 patients with chronic kidney disease (creatinine clearance, 15 to 50ml/min), with entry hemoglobin concentrations ([Hb]) of 110to

120 g/L (female patients) or 110 to 130 g/L (male patients).Patients were monitored for 2 yr or until they required dialysis; the patients were randomized to receive epoetin α as necessary to maintain Hb between 120 and 130 g/L (group A) or between 90 and 100 g/L (group B). The changes in LV mass index for the groups during the 2-yr period were not significantly different. There was no significant difference between the groups in 2-yr mean unadjusted systolic BP. The decline in renal function in 2 yr also did not differ significantly between the groups. In conclusion, maintenance of Hb above 120g/L, compared with 90 to 100 g/L, had similar effects on the LV mass index and did not clearly affect the development or progression of LV hypertrophy. The maintenance of Hb above 100 g/L for many patients in group B might have been attributable to the relative preservation of renal function.

5 Gary sirken et al (2003) conducted a retrospective study on "Erythropoietin requirements in maintenance hemodialysis patients with statin therapy".

It included 70 patients and was grouped into two. Patients initiated on statin therapy after the incident hemodialysis were included as study group 1 and group 2 patients were randomly selected (Non-statin therapy). Serum lipid panel, Hb, was monitored monthly. When analyzing Group1, statistical improvement in cholesterol, Hb, ferritin, EPO requirements, and albumin was noted after initiation of statin therapy. Mean values for lipid panel showed reductions in cholesterol, triglyceride, and LDL as well as elevation in HDL.Hb increased significantly ($p<0.0005$) after initiation of statin therapy.EPO requirements decreased by 25.1% after the introduction of statin therapy. Surrogate markers of inflammation (serum ferritin and albumin) significantly improved with statin therapy.

6. ***J.P Cristol*** et al (1997) as conducted a study on the topic "Erythropoietin and oxidative stress in hemodialysis : beneficial effects of vitamin E supplementation".

42 chronic hemodialysis patients (mean age of 60 +/-10 years) on renal replacement therapy for more than one year were included in this study. 12 patients of the whole group were regularly receiving subcutaneous erythropoietin. Patients treated with erythropoietin were systematically supplemented with parenteral iron; to maintain or replete their reserves. The results of lipid metabolism and oxidative stress parameters obtained in dialysis patients were compared to a control group of 38 healthy volunteers. The oxidative stress parameter was Malonyldialdehyde (MDA).erythrocyte vitamin E concentrations were decreased in hemodialysis patients treated with erythropoietin. It may be due to direct effect from erythropoietin or as a consequence of iron supplementation.

CONCLUSION

Many studies examining mortality and morbidity rates among patients with CKD have identified high rates of cardiovascular events. When even mild renal insufficiency is associated with other risk factors for cardiovascular disease, the risk of subsequent cardiovascular events is significantly increased.HDL have an antiatherogenic effect. With administration of erythropoietin there is an improvement in tissue oxygenation and overall increase in HDL biogenesis. This review concluded that in addition to the effect in anemia of renal disease erythropoietin have other beneficial effects like its influence in HDL biogenesis.

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