Original Article

Effect of Erythropoietin Stimulating Agents on Cardiovascular Events in Chronic Kidney Disease Patients on Hemodialysis

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Abstract

Objectives: Patients with chronic kidney disease (CKD) develop anemia which is treated with erythropoietin-stimulating agents (ESAs). However, ESAs do not reduce the risk of cardiovascular mortality. Furthermore, this is unclear whether ESAs therapy has any association with adverse cardiovascular events.

Methods: After an informed consent 275 male and female patients, between ages 35 to 75 years, with CKD stage V on ESAs undergoing twice weekly hemodialysis were enrolled. The dose of ESAs was calculated according to weight as 50mg/kg with target hemoglobin being 11 – 12 g/dl. Dose adjustments were made in the patients who failed to achieve target hemoglobin. The patients were followed for a year with the primary end point being new evidence of acute myocardial infarction (MI) diagnosed through ECG or echocardiography. Safety outcomes included stroke or death.

Results: The data was entered and analyzed in Statistical Package for Social Sciences (SPSS) version 18. Out of 275 patients, 164 (59.6%) patients were males and 111 (40.4%) were females. Mean age of the patients was 51.52 with standard deviation of ± 5.73. According to the results, 52 (18.9%) patients reported with MI and 223 (81.1%) patients had no evidence of MI. Out of 52 patients who had MI, 37 (71.1%) were males and 15 (28.8%) patients were female.

Conclusion: ESAs are associated with an increased risk of MI in CKD patients on hemodialysis. Whether there is a direct association or there are other factors involved remains to be seen.

Keywords: Chronic Kidney Disease, Erythropoietin stimulating agents, Myocardial Infarction, Anemia.

Introduction

Chronic kidney disease (CKD), caused by diabetes mellitus, hypertension and other diseases, is characterized by a progressive decline in the estimated glomerular filtration rate (eGFR); the diagnosis is confirmed via a reduced GFR for a minimum of 3 months often accompanied by albuminuria.[1,2] In CKD stage V characterized by total or near-total loss of kidney function, there is accumulation of fluid and toxic substances and patients require hemodialysis or transplantation to sustain their life and daily activities.[2-4]

The decrease in the production of erythropoietin, caused by renal insufficiency and the antiproliferative effects of the uremic toxins being accumulated in the body, results in anemia of chronic kidney disease.[5] In patients with CKD, who are receiving maintenance hemodialysis, treatment of anemia to achieve hemoglobin levels of 11 – 12 g/dl with the use of erythropoietin stimulating agents (ESA) leads to correction of the anemia and elimination of the need for blood transfusions albeit with an increased incidence of potentially fatal adverse effects.[5-8] The present study was

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All Authors have contributed in Study Design, Data Collection, Data Analysis, Data Interpretation, Manuscript Writing and Approval.

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designed to find out the risk of adverse cardiovascular events associated with ESAs therapy.

Patients and Methods

During this descriptive case series study, CKD stage V patients, aged between 35 – 75 years (both males and females) who were receiving ESA therapy for partial correction of hemoglobin, were enrolled after an informed consent. These patients were undergoing hemodialysis twice a week (each session lasting for 4 hours) for a period of less than 1 year.

The patients who had been on maintenance hemodialysis for a longer duration than a year, had a known coronary artery disease as evidenced by Coronary Angiography, previous episode of Myocardial Infarction established through fresh and previous ECG recordings or with the help of echocardiography or a known case of Left Bundle Branch Block (LBBB) were excluded. Pregnancy and Diabetes Mellitus were considered as additional criteria for excluding the patients from our study.

Patients were given human recombinant erythropoietin intravenously twice a week after every dialysis. The dose was initiated according to the weight as 50 mg/kg to achieve partial correction of hemoglobin however dose adjustments were made in those cases who failed to achieve target hemoglobin as per KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease by National Kidney Foundation. Target hemoglobin was set at 11 – 12 g/dl with a monthly increase in hemoglobin between 0.66 to 1 g/dl. The dose was reduced in cases where the rise in hemoglobin was beyond the monthly target.

The patients were routinely investigated for hemoglobin level at monthly interval and dose adjustments were made where necessary. Electrocardiogram (ECG) was routinely recorded at specified monthly intervals and at random intervals to record any active or recent ischemic changes. Echocardiography was routinely performed at 3 monthly intervals to look for signs of new onset segmental wall motion abnormalities.

The patients were followed up for a year with the primary end point being new evidence of acute myocardial infarction (MI). The secondary end point was evidence of echocardiographic changes of new segmental wall motion abnormality, intolerance to ESA therapy or drug related side effects leading to discontinuation of therapy. Safety outcomes included evidence of new episode of stroke, pericarditis or mortality.

Results

N	275
Mean	51.52
Std. Deviation	5.7352

Baseline Characteristics	ESRD Patients N=275
Age (years)	51.52 (± 5.73)
Sex – no. (%)	
Male	164 (59.6)
Female	111 (40.4)
Myocardial Infarction – no. (%)	
Yes	52 (18.9)
No	223 (81.1)

Myocardial Infarction	Frequency	Percent (%)
Yes	52	18.9
No	223	81.1
Total	275	100.0

The patients who were enrolled with ESRD were aged between 35 to 75 years. Mean age of the patients was recorded as 51.52 with the standard deviation of ± 5.73 as shown in table.

Out of 275 patients 164 (59.6%) patients were males and 111 (40.4%) were females. Patients, assessed for Myocardial Infarction (MI), were without known coronary artery disease or previous MI.With 95% Confidence Interval, it was observed that out of 275 patients of ESRD, only 52 (18.9%) patients were reported with MI, 223 (81.1%) patients did not report any incident of myocardial infarction. And it was also observed that out of 52 patients who had Myocardial Infarction, 37(71%) were males and 15(29%) patients were female.

It means only 18.9% End Stage Renal Disease patients were having Myocardial Infarction in ESA Therapy on Maintenance Hemodialysis and for male ESRD patients, the ratio of having Myocardial Infarction is high.

Discussion

The incidence of anemia of chronic disease or iron deficiency anemia is high considering the fact that these patients are erythropoietin or iron deficient. The landmark study by Obrador et al showed that among predialysis patients, 68% of those with advanced chronic kidney disease who required renal replacement therapy had a hematocrit less than 30 mg/dL; of these, 51% of patients had a hematocrit less than 28 mg/dL.[9] This warrants the use of ESA in most of these patients for partial correction of hemoglobin.[10,11]

The descriptive case series of 275 patients showed that 164 (59.6%) patients were males and 111 (40.4%) were females. The patients who were enrolled had their ages varying from 35 to 75 years with the mean age of the patients being 51.52 with the standard deviation of ± 5.73. Only 52 (18.9%) patients were reported with Myocardial Infarction and 223 (81.1%) patients did not have any evidence of Myocardial Infarction. It was also observed that out of 52 patients who had Myocardial Infarction, 37 (71%) were males and 15 (29%) patients were female. It means 18.9% of the total study population had myocardial infarction while receiving erythropoietin stimulating agents during a one year follow up period with a higher risk of myocardial infarction in male patients.

Literature review shows that The Normal Hematocrit Study tested the hypothesis that normalization of the hematocrit as compared to partial correction would improve cardiovascular outcomes. The Normal Hematocrit Study enrolled a total of 1233 patients between October 27, 1993, and March 31, 1996; 618 were assigned to the normal-hematocrit group, and 615 to the low-hematocrit group. After 29 months, there were 183 deaths and 19 first nonfatal myocardial infarctions among the patients in the normal-hematocrit group and 150 deaths and 14 nonfatal myocardial infarctions among the patients in the low-hematocrit group.[12] When compared with our study, the results show a relatively similar trend of myocardial infarction albeit with a higher incidence since we recorded 52 incidences of myocardial infarction with 37 of those being males and 15 females (71% and 29% respectively). A high incidence of myocardial infarction in this study which is in accordance with the results of NHS translates into a more cautious approach when advising or continuing the use of ESA with a greater emphasis on monitoring the adverse effects after initiation of such treatment protocols.[13-15] Regular screening protocols need to be established for this patient population with a careful selection of patients for these treatments.[16]

A limitation of our study was that we did not rule out other causes of coronary artery disease in the patients who were reported to have myocardial infarction during the observation period like atheroscleorsis caused by dyslipidemia or advanced atherosclerosis due to any cause.[17,18]

Conclusion

We found that the use of ESA in end stage renal disease patients who are on regular maintenance hemodialysis is adversely related with myocardial infarction. The use of ESA should therefore be carefully monitored to avoid potentially fatal outcomes. Whether this is the only contributing factor in this population or there are other factors related to this finding should be further investigated through a multi-centre study that includes other causes of myocardial infarction as part of the study design.

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