

Original article:

Impact of correction of anemia on major complication of chronic renal diseases

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Abstract:

Objective: To assess the impact of correction of anemia on the major complication of Chronic renal disease (CRD).

Methodology: A prospective study evaluating the correction of anemia in CRD patients with recombinant human erythropoietin (rHuEPO) over a period of one year. Ejection fraction (EF), left ventricular mass index (LVMI), mini-mental status examination (MMS), cognition, focal neurodeficit and general sense of wellbeing (GSW) were measured by echocardiography, and appropriate scales on admission respectively at 3 months and 6 months follow-up to find out the hemodynamic changes that could be achieved by correction of anemia.

Results: Statistically strong significant ($P < 0.001$) improvement of hemoglobin level occurred with rHuEPO therapy in the overall population, both at 3 month and 6 month follow-up. Statistically significant ($P < 0.05$) improvement of EF occurred at 6 months follow-up in total population. At 6 months follow-up, there was significant change ($P = 0.015$) of LVMI in total population. Even at 6 months follow-up, there was no significant change in the MMS ($P = 0.66$) and cognition ($P = 0.20$) of the study population, but significant improvement ($P < 0.001$) of GSW occurred among the study population. There was also positive correlation between improvement of anemia with improvement of EF at 3 months follow-up ($r = 0.531$).

Conclusion: Correction of anaemia, even if partial, causes significant improvement in cardiovascular function as evidenced by increase in EF, even at short term follow-up of 6 months in our study. Anaemia of CRD also have an impact on neurological and GSW.

Keywords: Chronic renal disease, Recombinant Human Erythropoietin, RBC, GFR, Haemodialysis.

Introduction:

The current diagnostic guidelines as published by National Kidney Foundation^[1] states that anaemia in chronic renal disease (CRD) can be diagnosed when haemoglobin is less than 11gm/dl in premenopausal women and less than 12gm/dl in men and postmenopausal women. Whereas the initial National Kidney Foundation k/DOQI anaemia guidelines specified a serum creatinine value of 2mg/dl as a benchmark to initiate investigation of anaemia^[1], the more recent CRD guidelines recommend surveillance testing for its presence in all patient with renal disease at a glomerular filtration rate (GFR) of less than

60ml/min/1.73m².^[2] The anaemia of renal failure is characterized by normocytic and normochromic red blood cell (RBC), the reticulocyte count is low for the degree of anaemia, and the erythroid bone marrow appears hypoplastic, without interference with leucopoiesis or megakaryocytopoiesis.^[3] Anaemia begins early in CRD^[3] at stage 3 of CRD (GFR of 30 to 59ml/min/1.73m²) and almost universal at stage 4 of CRD (GFR of 15 to 29ml/min/1.73m²). Anaemia of CRD develops earlier in diabetic nephropathy. Anaemia initially is mild however as renal function progressively deteriorates, the haematocrit continues to decline and may reach concentration as low as 15 - 20%, at

that point, the patient usually experiences symptoms and transfusion may be necessary.^[3] The anaemia of renal failure is a complex disorder determined by a variety of factors.

The leading cause of anaemia in patients with CRD is inadequate production of endogenous erythropoietin by the impaired kidneys.^[1]

A number of other factors may play contributory roles. Some degree of haemolysis is frequently present. Gastrointestinal blood loss commonly due to telangiectasia and angiodysplastic lesions may contribute to anaemia in patients with advanced CRD.^[4] Platelet abnormalities may also prolong bleeding time. Toxic metabolites (uremic toxins) has been assumed to inhibit erythropoiesis either directly or by interfering with the action of erythropoietin(EPO) and haematopoiesis-stimulating-cytokines,if the patient is iron deficient (transferrin saturation <20%, and serum Ferritin <100 mg/L), then administer iron, 50-100 mg intravenous twice per week for 5 weeks, if iron indices are still low, repeat the same course. Withhold iron therapy when transferrin saturation is >50% and/or ferritin > 800 ng/ml.^[1,5,6] If patient is on intravenous iron replacement therapy,monitoring serum ferritin and transferrin saturation, total iron binding capacity and serum iron every 3 monthly.^[1,5,6] Renal anaemia is rapidly corrected by rHuEPO therapy, but doses required can vary greatly^[7] ranging from 50 to 300 IU/Kg three times per week. Doses exceeding 300 IU/kg three times per week do not enhance the erythropoietic response.^[7] The dosage of rHuEPO must be adjusted monthly until the target is attained. Good improvement in quality-of-life scores has been shown with EPO therapy in pre-dialysis patients as well as patients on maintenance HD. Fatigue disappears and sense of well-being increases.^[8]

Methods:

A prospective study was conducted in the Department of General Medicine in N.R.S. Medical College & Hospital Kolkata, India, over a period of one year to assess the impact of correction of anaemia on major complication of CRD. Like anaemia there are so many complication in CRD, we want to study the impact of anaemia correction on the major complications of CRD. In our study, correction of anaemia in CRD patients was done with recombinant human erythropoietin (rHuEPO) and ejection fraction(EF), left ventricular mass index (LVMI), mini-mental status examination (MMS), cognition, focal neurodeficit and general sense of wellbeing (GSW) were measured by echocardiography, and appropriate scales on admission, at 3 months and 6 months follow-up to find out the hemodynamic changes that could be achieved by this correction of anaemia.

All patients had routine clinical follow-up including body weight measurement, evidence of systemic and pulmonary oedema if any, urine output, pulse rate, blood pressure measurement, fortnightly/ monthly and as on need basis. Hemogram including reticulocyte count every fifteen days with blood urea nitrogen (BUN) and urinalysis more vigorously in certain selected high risk cases. In addition all had clinical and necessary investigational check up on their cardiovascular status along with vigil on any complications arising out of rHuEPO therapy.

Statistical analysis was done on individual parameters viz. Hb%, LVMI, MMS, cognition and GSW. Statistical significance of the parameters between three time points was estimated by using ANOVA with multiple comparison Bonferroni method and correlation between corrected haemoglobin level and subsequent changes in EF, LVMI, MMS, cognition and GSW were analysed

through correlation coefficient using Pearson's correlation test.

Results:

In our study subjects, 53.33% were male and 46.67% were female. In the study population, around 70% patients had initial creatinine level of > 2 mg/dl. Through administration of recombinant human erythropoietin (rHuEPO), in 25% cases, the target hemoglobin (11gm/dl in premenopausal female and 12gm/dl in male and postmenopausal female) was achieved and in 50% cases, the hemoglobin could be corrected unto the range of 9 to 11 gm/dl and in 25% cases no improvement in the hemoglobin level could be achieved.

In this study, the female patients had a lower hemoglobin on admission than male patients and responds with rHuEPO was almost same in both sexes, both at 3 months and 6 months follow-up. Statistically strong significant ($P < 0.001$) improvement of hemoglobin level occurred with rHuEPO therapy in the overall study population, both at 3 and 6 months follow-up. Statistically significant ($P < 0.05$) improvement of EF occurred at 6 months follow-up in total population. At 6 months follow-up, significant change ($P = 0.015$) of LVMI in total population. (Table 1) However at 6 months follow-up, there was no significant change in the MMS ($P = 0.66$) and cognition ($P = 0.20$), (Table 2), of the study population but significant improvement ($P < 0.001$) of GSW occurred among the study population. (Table 3). There was also positive correlation between improvement of anemia with improvement of EF at 3 months follow-up ($r = 0.531$). (Table 4).

Discussion:

It is an established fact that anemia in CRD is primarily caused by relative erythropoietin deficiency.^[9,10] Anemia generally develops when renal function decreases below 50% of normal^[9,10] Among the multiple pathophysiologic disturbances

of CRD, the most important are the cardiovascular effects which includes left ventricular hypertrophy (LVH), left ventricular dilatation (LVD), congestive cardiac failure (CCF) and these are the main causes of mortality in CRD.^[11,12]

Numerous small studies have shown that even partial correction of anemia with rHuEPO has resulted in a decrease in left ventricular mass and volume in the range of 15% to 30%.^[13-16] Treatment of anemia with rHuEPO has also been associated with improvement in cognition and quality of life in CKD patients.¹² This prospective study was conceived to show the impact of anemia correction on major complications of CRD. In our study, in contrast to the studies carried out in the western world, around 70% patients had initial Creatinine level of > 2 mg/dl. But even then a complete correction of anemia could be achieved in around 25% of patients and partial correction of anemia in 50% of patients. Statistically significant improvement of anemia was achieved at 3 months and 6 months follow-up ($P < 0.001$) with significant improvement of EF, LVMI and GSW at 3 months and 6 months follow-up. However no significant change for cognition and mini mental status (MMS) even at 6 months follow up. All the major clinical trials done previously have shown statistically significant decrease in LVD, increase in EF and decrease in LVMI but in most of them they had a successful follow up of around five to ten years.^[13-16]

Conclusion: It is established that anemia in CRD is primarily caused by relative erythropoietin deficiency.^[8,9] Anemia generally develops when renal function decreases below 50% of normal.^[8,9] Among multiple pathophysiologic disturbances of CRD, the most important are the cardiovascular effects which includes LVH, LVD and CCF. The cardiovascular disturbances associated with anaemia of CRD are set in motion even before

CRD manifest clinically and/or biochemically.^[11,12] Thus anaemia is an independent risk factor for surrogates of CVD such as LVH, LVD and CCF . Correction of anaemia, even if partial, causes significant improvement in cardiovascular function

as evidenced by increase in EF, even at a short term follow up of 6 months in our study. Anaemia of CRD also have an impact on neurological and GSW.^[17,18]

Table 1: Clinical Characteristics of Study Patients

Variable	Admission, N=30		3 months, N=20		6 months, N=20	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
Hemoglobin	7.99	1.49	9.52	1.73	9.71	2.21
Ejection Fraction	56.93	10.61	57.75	12.65	57.75	12.20
LVMI	99.43	7.83	98.40	8.22	98.10	8.06
Mini Mental State	29.43	0.63	29.25	0.85	29.30	0.80

left ventricular mass index

Table 2: Table of Cognition

Table of Cognition				
	Mild cognitive impairment	Moderate cognitive impairment	Normal cognition	Total
Admission	16 (n)	0 (n)	14 (n)	30 (n)
	53.33 %	0 %	46.67 %	
3 months	10 (n)	0 (n)	10 (n)	20 (n)
	50 %	0 %	50 %	
6 months	5 (n)	1 (n)	14 (n)	20 (n)
	25 %	5 %	70 %	
Total	31 (n)	1 (n)	38 (n)	70 (n)

n- number of patients, % - percentage of patients

Table 3: General Sense of well-being

	Table of General Sense of Well being			Total
	No wellbeing	Normal well being	Some amount of Wellbeing	
Admission	4 (n)	0 (n)	26 (n)	30 (n)
	13.33%	0%	86.67%	
3 months	2 (n)	1 (n)	17	20 (n)
	10%	5%	85%	
6 months	0 (n)	9 (n)	11 (n)	20 (n)
	0%	45%	55%	
Total	6 (n)	10 (n)	54 (n)	70 (n)

n- number of patients, % - percentage of patients

Table 4: Correlation between Clinical Characteristics

Correlation between Hb, EF and LVMI on admission	Correlation between Hb, EF and LVMI at 3m follow up	Correlation between Hb, EF and LVMI at 6m follow up
Baseline Hemoglobin & Baseline Ejection fraction r = 0.054	Hemoglobin at 3 months & Ejection fraction at 3months r = 0.531	Hemoglobin at 6 months & Ejection fraction at 6 months r = 0.359
Baseline Hemoglobin& Baseline LVMI r = 0.156	Hemoglobin at 3 months and LVMI at 3 months r = 0.134	Hemoglobin at 6 months & LVMI at 6months r = 0.255

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