
The Effect of Erythropoietin Treatment on Left Ventricular Hypertrophy in Haemodialysis Patients

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Abstract

Anaemia appears to play an important role in left ventricular (LV) enlargement in chronic kidney disease patients.

The objective of this study was to evaluate LV echocardiography changes during anaemia correction with recombinant human erythropoietin (rHu-Epo) in chronic haemodialysis patients (HD pts) with signs of anaemia and LV hypertrophy (LVH).

The study included 20 HD pts aged $39,6 \pm 5,3$ yrs, with the same condition of HD treatment, anaemia and echocardiographically LVH verified. At the beginning of the rHu-Epo treatment haemoglobin (Hb) level was < 90 g/L and the target Hb level was 110 g/L. Echocardiography was performed at the beginning (baseline) and after six months of rHu-Epo treatment. LVH was defined as LV mass index >100 g/m² in women and >131 g/m² in men.

We observed significant reduction of LV mass index (LVMI) (mean 26,4%, $p=0.008$), as well as LV volumen. There was a significant negative correlation between Hb level and LVMI with predictive LVMI reduction of 2,317 g/m² for each 1g/L rising of mean Hb level.

The results of the study confirm the importance of early anaemia correction in haemodialysis patients aimed to improve LV parameters.

Introduction

Cardiovascular complications are the leading cause of mortality in the end stage renal disease and are responsible for about 50% of total mortality rate of uraemic patients treated by dialysis (1,2).

Incidence of cardiac death is 10 - 20 times higher in these patients than in general population of the same age (3). Hypertrophy of left ventricle is especially related to high mortality rate of uraemic patients (4) and is considered as an independent risk factor.

Anaemia presents a proven factor related to cardiac abnormalities within these group of patients (5,6). It is mostly mediated by the lack of erythropoietin, a hormone produced by type I fibroblasts of peritubular inter-

stitium and epithelial cells of proximal tubules, which is the key regulator of erythropoiesis. There are two main peripheral effects of anaemia which strongly reduce total peripheral resistance. One of them is the reduction of blood viscosity, related to diminished concentration of erythrocytes, and the other is lower tissue oxygen delivery due to lower haemoglobin level. Lower oxygen delivery leads to local vasodilatation, which significantly increases ventricular preload and cardiac output, as a compensatory mechanism of reduced capacity for oxygen transport. The increment of cardiac output aimed to satisfy metabolic needs has also significant impact to LV geometry.

Aim

The aim of the study was to analyse LV echocardiographic changes in the course of anaemia correction by human recombinant erythropoietin (rHuEpo) in haemodialysis patients (HD pts) with expressed anaemia and left ventricular hypertrophy (LVH).

Subjects and methods

This prospective study included the group of 20 HD patients, aged $39,6 \pm 5,3$ years, with the same duration and conditions of chronic haemodialysis treatment, performed at the Institute of Nephrology of Clinical Centre University of Sarajevo (renal replacement treatment started within 2 years of the beginning of the study, with dialysis performed 3 times weekly for a period of 4 hours, using machines with controlled ultrafiltration rate and biocompatible dialysers, A - V fistule as a vascular access, and with adequate dialysis delivery dose). The patients included fulfilled the following criteria: stable clinical status, haemoglobin levels < 90 g/L, negative history for blood loss and previous application of human recombinant erythropoietin, and with echocardiographic signs of LVH.

Human recombinant erythropoietin was applied subcutaneously in the period of six months, beginning with 50 IU/kg of body weight (BW), three times per week after dialysis treatment, until achievement of desired haemat-

ocrit of 35% and haemoglobin levels of 110 g/L. In the maintenance phase the dosage was reduced to 25-50 IU/kg of BW 1-2 times per week.

Criteria for discontinuation of erythropoietin treatment were: high blood pressure values (> 150/90 mmHg) and thrombosis of A - V fistule.

Each participant had the echocardiography performed, at the beginning of the study and after the treatment undertaken in the period of 6 months. It was done at the Department of Cardiology of Clinical Centre University of Sarajevo by a cardiologist who was not familiar with the clinical status of the patients and the phasis of the undertaken treatment. The instrument used was equipped with transducer of 2.5 MHz, which allows M-mod, as well as two-dimensional and pulsatile Doppler measurements. Echocardiograms were always done with achieved "dry" body weight of patient, within 24 hours after the latest haemodialysis performed, with the aim to avoid the increment of internal LV diameter due to increment of blood volume related to liquid intake and loss of excretory renal function. Namely, the LV mass index measured before dialysis is higher up to 25 g/m² as compared to postdialysis measurement, although the actual left ventricular mass remains unchanged (7).

Statistical analysis

LV mass was calculated according to Devereux's modified cubical formula of American Association of Cardiologists:

$$\{0,00083[(LVEDD+IVS+PW)^3-(LVEDD)^3]+0,6\} /BSA.$$

Criteria for LV hypertrophy were the following: LV mass index higher than 131 g/m² in males and higher than 100 g/m² in females (8).

Differences between the gathered parameters were analysed using paired Student t test on the level of sta-

tistical significance of p<0.05.

Correlation of observed variables was assessed using Pearson's correlation test with the significance level of p<0.05. Linear regression test (β coefficient) was used to determine an independent association of LVH as an criterium with mean haemoglobin level as an predictor.

Results

The impact of erythropoietin treatment on biochemical indicators of anaemia is presented in Table 1, and effect of this drug in correction of renal anaemia can be clearly seen.

Efficient correction of anaemia led to significant reduction of LV mass index in these patients (p=0.008), achieving normal values in few patients (Table 2). Changes in LV volume were also echocardiographically noted and were very close to anticipated statistical significance (p=0.072).

We observed significant correlation of haemoglobin levels and echocardiografic changes of LV (Table 3), with prediction of significant reduction of LV mass index for 2,317 g/m² for each increment of 1 g/L of haemoglobin value (Table 4). We observed higher reduction of LV posterior wall thickness in comparison to interventricular septum.

Discussion

Mechanisms of cardiovascular adaptation in anaemia were clearly reported in experimental animal studies, as well as in humans with severe deficit of vitamin B12, iron or folats. The key haemodinamic change in chronic anaemia is a hyperkinetic state, which is obvious when the haemoglobin levels falls below 70 g/L. In relative tissue hypoxia, cardiac output is increasing in order to meet metabolic demands. Therefore, many authors tried to emphasise anaemia as a factor important in structural adaptation of myocard, particularly in development of

Table 1. The impact of erythropoietin treatment on anaemia indicators

	Erythrocytes (x 10 ¹² /L)	Haematocrit (%)	Haemoglobin (g/L)
Baseline values	2.02 ± 0,23	18.9 ± 1.9	69.0 ± 9.4
After 6 months treatment	3.25 ± 0.36	30.6 ± 2.7	107.0 ± 11.3
Difference	+ 60.5%	+ 62.8%	+ 55.1%
p value	<0.001	< 0.001	<0.001

Table 2. The impact of erythropoietin treatment on lv mass index and lv volume

	LV mass index (g/m ²)	LV volume (ml/m ²)
Baseline values	208.1 ± 76.6	101.25 ± 33.6
After 6 months of EPO treatment	153.2 ± 55.9	83.07 ± 25.0
Difference	- 26.40%	- 17.95%
P value	0.008	0.072

Table 3. Correlation of haemoglobin level and lv mass index during epo treatment

	Haemoglobin (g/L)	LV mass index (g/m ²)
After EPO treatment	107.0 ± 11.3	153.2 ± 56.0
r (correlation coefficient)	0.47	
p - value	0.038	

Table 4. Haemoglobin (hb) level as a predictor of lv mass index (lvmi) during erythropoietin therapy

Outcome	Association	β coefficient	p value
LVMI reduction for 2.32 g/m²	Each increment of 1 g/L of average Hb level	0.466	0.038

LV hypertrophy, with still unanswered question regarding the level of haemoglobin associated with increment of LV mass index.

Levin and associates (9) showed that the risk for HLV rises with the fall of haemoglobin levels in predialysis patients with higher prevalence of anaemia in patients with eccentric LVH as compared with concentric LVH or those without LV hypertrophy.

In our study erythropoietin treatment in a 6 months period resulted in average reduction of LV mass index of 26,4%, but individually higher reduction was achieved in patients with initially higher LV mass index. We also noted higher reduction of LV posterior wall thickness in comparison with interventricular septum. We found sig-

nificant correlation regarding the level of haemoglobin and echocardiographic changes (p=0.038). Each increment of 1 g/L of average haemoglobin level was associated with significant reduction of LV mass index for 2,317 g/m² (p=0.038).

Silberberg et al. (10) achieved 15% reduction of LV mass in 6 months period of erythropoietin treatment in 22 patients. In Wizemann's study (11) partial correction of anaemia (achievement of haematocrit value of 35%) resulted in reduction of average LV mass index from 199 to 173 g/m² in 4 months erythropoietin treatment (p < 0.01), and further reduction of 160 g/m² was achieved in 16 months (p < 0.001). Similar results were reported in some other echocardiographic studies in patients with chronic renal failure treated with erythropoietin, which

included 12 - 25 patients observed in a period of 12 - 78 weeks (12, 13, 14). It is not surprising that reduction of LVH achieved with erythropoietin was incomplete, having in mind long term development of LVH, association with interstitial fibrosis, continuous presence of other factors contributing to uraemic cardiomyopathy and possibly to the fact that correction of anaemia is not sufficient.

It is well known that development of hypertrophy and dilatation of the left ventricle, as an "adaptive" response to hypoxia, is undoubtedly deleterious, as these patients have reduced coronary reserve which makes them predisposed to arrhythmias, myocardial infarction and myocardial fibrosis. Therefore it is not surprising that combination of anaemia and LVH is associated with increased cardiac risk and sudden death in these patients. For that reason, prevention of hypertrophy or timely reduction of LV mass index by pharmacological influence to potentially reversible factors, such as anaemia, is of crucial importance.

Conclusions

1. Uraemic cardiomyopathy is dependant on many risk factors, whose association and long term influence is characteristic for chronic renal failure
2. Anaemia is considered to be one of the potentially reversible cardiac risk factor in chronic haemodialysis patients.
3. Correction of anaemia with erythropoietin leads to significant partial regression of LV hypertrophy.
4. Control of known risk factors are aiming to prevent myocardial damage and achievement of cardiovascular stability of haemodialysis patients.

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