Erythropoietin therapy in chronic renal failure patients prior to hemodialysis

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Submitted: 11 January 2005
Accepted: 4 April 2005

Arch Med Sci 2005; 1, 1: 55-58

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Abstract

The human recombinant erythropoietin (hrEpo) is crucial in anemia treatment options in chronic renal failure patients undergoing regular hemodialysis therapy. However, the clinical characteristics of erythropoietin treatment prior to hemodialysis have not been thoroughly studied. This study was aimed to analyze in retrospective manner the results of hrEpo therapy in chronic renal failure prior to hemodialysis. The study included 42 patients (26 males and 16 females, 42.4±3.7 yrs old) with mean serum creatinine 305±32 µmol/l, whose anemia and iron homeostasis parameters were carefully assessed. HrEpo improved both the general state of the patients and the life quality, it decreased cardiovascular complications and the mortality of patients prior to hemodialysis therapy. Iron supplementation during erythropoietin therapy was required, in the majority of patients oral iron was sufficient. The application of human recombinant erythropoietin prior to hemodialysis is a safe option, it does not accelerate the progression of chronic renal failure, only in a small number of patients moderate increase of blood pressure was noted that could have been effectively managed with the modification of doses of hypotensive pharmacotherapy.

Key words: chronic renal failure, predialysis anemia, recombinant human erythropoietin.

Introduction

Anemia is the most common complication in chronic renal failure that significantly affects the patients' quality of life [1-5]. It becomes clinically relevant at creatinine clearance level of 40 ml/min, and it is evident at the clearance decrease down to 25 ml/min [6]. The origins of anemia in chronic renal failure patients include: decreased release of erythropoietin, circulating inhibitors of erythropoiesis (uremic toxins), hemolysis, iron, vitamin B12, B6, folic acid deficiency, chronic inflammatory states, toxic effects of aluminum. The most relevant deficiency is however, related with the decrease of erythropoietin production in the kidneys [4]. The introduction of human recombinant erythropoietin was a crucial step in anemia treatment options in chronic renal failure patients undergoing regular hemodialysis therapy [7, 8]. It markedly limited the requirements for blood transfusion in these patients. The satisfactory effects of anemia therapy in patients with chronic renal failure on regular hemodialysis led to the introduction of erythropoietin prior to hemodialysis [9]. Contemporary clinical results indicate beneficial effects of human recombinant erythropoietin in patients prior to hemodialysis therapy [10, 11].

Table 1. Clinical characteristics

Parameter	EPO patients n=42	Control group n=24
Age (years)	42.4±3.7	45.8±3.5
Gender (M/F)	26/16	14/10
Serum creatinine (µmol/l)	305±32	880±70
Serum urea (mmol/l)	15.1±3.8	32.9±3.8
Kidney disease		
Glomerulonephritis	10	5
Pyelonephritis	8	4
Diabetic nephropathy	10	6
Polycystic kidney disease	4	3
Hypertensive nephropathy	6	3
Others	4	3

This study was aimed to analyze in retrospective manner the results of hrEpo therapy in patients with chronic renal failure prior to hemodialysis admitted to Outpatient Nephrology Department, Medical University Hospital No. 2, Medical University of Lodz from 2001 to 2004.

Material and methods

The study included 42 patients with chronic renal failure on erythropoietin therapy. The control group included 24 patients with chronic renal failure treated with hemodialysis as an emergency without any previous care on an outpatient basis. The clinical characteristics of both groups are depicted in Table 1.

The inclusion criteria for erythropoietin treatment were defined as anemia parameters in the following range: hemoglobin <10 g/dl, hematocrit <33% and renal function impairment as assessed with glomerular filtration rate GFR <30 ml/min (in diabetic patients GFR <45 ml/min) after exclusion of iron deficiency, chronic blood loss and anemia causing disease states.

All subjects included into the study expressed their informed consent before study enrolment. The patients were administered with human recombinant erythropoietin once to thrice a week subcutaneously after they were qualified to undergo regular hemodialysis, mean erythropoietin dose was 4700±1700 IU per week, mean duration of erythropoietin therapy was 49±18 weeks. At the time of erythropoietin therapy, patients received oral supplementation of iron (Sorbifer durules, Hemofer prolongatom, Ferrum Lek) at the dose 1-3 tablets a day, 14 patients (33%) required intravenous administration of iron formulas (Ferrum Lek, Venofer) from 5 to 30 ampules, mean 9.5±1.1 ampules.

Each patient was monthly screened to monitor blood morphology, serum creatinine, urea, electrolytes, proteinogram as well as their reticulocytosis, iron, ferritin, total iron binding capacity (TIBC) were assessed every three months.

In the statistical analysis, results are expressed as arithmetic mean standard deviation. Wilcoxon rank sum test was used for the comparisons among study groups, and Wilcoxon test was used to compare the data within a group. Differences were statistically significant if $p<0.05$.

Results

The clinical parameters assessed are presented in Table 2.

Discussion

The first reports on the application of human recombinant erythropoietin as a treatment option in anemia in chronic renal failure patients on regular hemodialysis appeared in mid 1990s [7, 8]. The clinical application of erythropoietin in anemia therapy allowed to reduce blood transfusions in these patients as well as it markedly improved their quality of life, decreased cardiovascular complications and the mortality [3, 12, 13]. The encouraging results of erythropoietin therapy in hemodialysis patients facilitate its introduction in chronic renal failure patients prior to hemodialysis [14]. However, some reports based on animal research model indicated probable progression of renal impairment during erythropoietin treatment prior to hemodialysis [15] apparently limiting its standard application in clinical settings. The following years brought more data confirming the safety and efficiency of erythropoietin in these particular groups of patients. The beneficial effects of erythropoietin in the treatment of anemia in non-dialyzed patients with chronic renal failure has been thoroughly established and the lack of any facilitation of renal failure progression was reliably confirmed in numerous studies [16-20]. The most up-to-date recommendations for anemia therapy in chronic renal failure emphasize that erythropoietin treatment should be started as soon as possible [20, 21]. The early introduction of erythropoietin treatment

Table 2. Clinical results

	Study group before EPO therapy	Study group after EPO therapy	Control group without EPO therapy
HCT (%)	25,1±2.5	31.5±3.8 • ▪	23.5±1.9
HGB (g/dl)	8.5±0.9	10.9±1.9 • ▪	7.5±0.9
RBC (10^6/mm^3)	3.1±0.4	4.0±0.5 • ▪	2.6±0.3
MCV (µm^3)	82±8.5	84±8.2	81±9.1
MCHC (g/dl)	31±3.5	33±3.5	30±3.9
Fe (µmol/l)	13.1±1.5	14.1±1.7	11.5±1.1
Ferritin (µg/l)	51±6.1	60±8.9	42±5.2
TIBC (µmol/l)	49.5±9.2	43.6±4.9 •	50.1±6.2

TIBC – total iron binding capacity
• p<0.05 in comparison to control values
▪ p<0.05 in comparison to values in patients prior to EPO therapy

was shown to decrease cardiovascular complications and reduce morality in both predialysis stage and the first year of hemodialysis [22]. It was related with the observations that anemia in chronic renal failure was a relevant factor associated with left ventricular hypertrophy and heart failure [23-26]. Following 2001 recommendations from national expert team in nephrology regarding management of anemia in non-dialyzed chronic renal failure patients, we started to include these patients into erythropoietin treatment program. Our own clinical data confirm high efficiency of erythropoietin treatment in this group of patients. The significant increase of hematocrit, hemoglobin concentration and red blood cell number were found in patients treated with erythropoietin in comparison to the initial parameters in the study group and control group values. Since iron deficiency may occur in chronic renal failure patients and lead to anemia [27], the iron homeostasis was verified and iron supplementation was introduced. Then, during erythropoietin administration, due to the increased iron requirement, oral iron supplementation was maintained (at the level of 100-300 mg elementary iron) under the control of standard lab tests. One third of the patients required intravenous iron supplementation due to side effects of oral iron or/and insufficient level of iron homeostasis, specifically 5 to 30 ampules of intravenous formulas. This group included patients treated with higher doses of erythropoietin or those treated for extended time period. This specific observation was also commonly encountered in previous studies [1, 28-30]. Additionally, during erythropoietin treatment, arterial blood pressure may increase [9]. The careful control and assessment of blood pressure is necessary especially in patients receiving large, intravenous doses of erythropoietin. However, since patients prior to hemodialysis commonly receive smaller, subcutaneous doses, blood pressure elevation in markedly less frequent. In our study, none among normotensive subjects experienced blood pressure increase and among those with preexisting arterial hypertension, only a fourth demonstrated the increase of blood pressure that required more intense hypotensive pharmacotherapy. These data are supported by other studies [2, 31].

Conclusion

1. The application of human recombinant erythropoietin to treat anemia in chronic renal failure patients prior to hemodialysis is currently a standard procedure.
2. HrEpo improves both the general state of the patients and the life quality, it decreases cardiovascular complications and the mortality, patients are entering hemodialysis therapy in a better general condition.
3. Iron supplementation during erythropoietin therapy is required, in the majority of patients oral iron is sufficient.
4. The application of human recombinant erythropoietin prior to hemodialysis is a safe option, it does not accelerate the progression of chronic renal failure, only in a small number of patients moderate increase of blood pressure is noted that may be effectively managed with the modification of doses of hypotensive pharmacotherapy.

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