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ErythRopoietin Hyporesponsiveness in Patients on Hemodialysis and Continuous Ambulatory Peritoneal Dialysis

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ABSTRACT

Chronic kidney disease (CKD) is a social and worldwide problem. Erythropoietin resistance is very common due to different reasons in patients with CKD, anemia on dialysis therapy. A prospective study was conducted evaluating the serum erythropoietin and ferritin levels in patients with CKD treated with dialysis within the scientific project №8/2024, funded by MU-Pleven. A total of 88 patients treated with hemodialysis and 12 patients treated with peritoneal dialysis (CAPD) were included. An analysis was made of the correlations between the serum levels of endogenous erythropoietin, ferritin levels with haemoglobin doses of recombinant exogenous erythropoietin, serum creatinine, URR and main renal disease. The anti-erythrocyte antibodies were also examined. The results show that in patients undergoing hemodialysis treatment the level of serum erythropoietin and ferritin are lower than levels in CAPD patients. There is no significant difference between the serum erythropoietin levels in patients from both genders. It was noticed that patients with lower EPO and ferritin levels are receiving higher doses of erythropoietin but low dose of iron weekly. In patients treated with CAPD the level of serum erythropoietin varies between 4.6 and 45.6 U/l, the average level of serum erythropoietin is significantly higher and the average age and duration of renal replacement therapy is significantly shorter compared to patients on hemodialysis.

We noticed versatile relations between the level of serum erythropoietin and the main markers for chronic renal failure and dialysis treatment. In any patient anti-erythrocyte antibodies have not been discovered.

Keywords: Erythropoietin; Renal Anemia; Chronic Kidney Disease; Dialysis; Erythropoietin Resistance

Abbreviations: CKD: Chronic Kidney Disease; ESRD: End-Stage Renal Disease; EPO: Erythropoietin; HB: Haemoglobin; EPO: Erythropoietin; RHUEPO: Recombinant Human Erythropoietin; HD: Hemodialysis; EPOR: Erythropoietin Resistance; EPOH: Hyporesponsiveness

Introduction

Chronic kidney disease (CKD) is a social and worldwide problem. CKD usually develops slowly in time, rarely with severe clinical symptoms until the end-stage kidney decease and usually associated with high morbidity, hospitalizations and mortality. When the renal function decline to end-stage renal disease (ESRD) must be replaced with hemo- or peritoneal dialysis, or transplantation. Anaemia is one of the most common complication in CKD. Renal anaemia is normocytic normochromic characterized by low levels of red blood cells, haemoglobin (Hb) is low due to insufficient production of erythropoietin (EPO) from the kidneys' parenchymal peritubular cells. Patients report shortness of breath, constant fatigue, and insomnia. The introduction of recombinant human erythropoietin (rHuEPO) for treatment of renal anaemia was a major breakthrough for these patients into

the 1980s. The usage of EPO/ESA improved this group of patients' life prognosis, morbidity, mortality. The ESA therapy in predialysis CKD patients delays time to start dialysis. The CKD patients on dialysis are receiving EPO. Back then before ESA impairment the only for anemia correction for ESRD patients on HD were the blood transfusions USRDS 2020 annual data report concluded that more than 85% of hemodialysis patients received EPO treatment [1]. The primary reason for less effective rHuEPO is loss or low iron. The iron deficiency is common in CKD influencing 50% of these patients [2].

Erythropoietin insufficiency in CKD patients is often connected also to underlying chronic inflammation, different comorbidities – diabetes, non-threated urine infection, etc. Anaemia in patients on hemodialysis (HD) is connected to additional factors like chronic blood loss, hemorrhages, impaired erythropoiesis, oxidative stress, chronic catheter infections. HD patients with untreated anemia can develop cardio-vascular complication such as left ventricular hypertrophy – due to decreased tissue oxygenation causing first tachycardia, vasodilatation, increased pump function, then heart failure, decreasing quality of life. Other secondary but not to be underestimated consequences are poor patient's compliance of HD, poor contribution and collaboration dialysis prescription. Erythropoietin resistance (EPOR) is common in patients with CKD, anemia on dialysis therapy. There isn't a global guideline on how to define EPOR. But also EPO hyporesponsiveness is lack of response of EPO therapy resulting in no elevation of Hb levels on usual weight-based dosing. Despite the administration of EPO at appropriate doses about 5-10 % of patients treated with HD develop EPOH [3]. Other authors defined EPOH as having no increase in Hb concentration from the baseline after the first month of treatment on appropriate weight-based dosing [4]. EPOR is more common in CKD patients on dialysis. EPO hyporesponsiveness (EPOH) still remains a difficult problem to be solved in nephrology practice worldwide.

EPOH worsens the prognosis, spatially in CKD patients who are starting dialysis in emergency way. Patients on dialysis with EPOH have poor prognosis and outcome, poor adaptation to dialysis. All types of patients on or non-dialysis have poor quality of life if they have EPOR. Different factors are associated with EPOR including iron deficiency, inflammation, severe uremia, non-effective dialysis treatment. EPOR is defined as a persistent anemia – Hb low than 10-12 g/dL – or need of very high dose of EPO/ESA – more than 300 IU/kg/weekly s.c. or 450 UI/kg/weekly i.v. The starting goal is achievement of Hb increase of 0.3 g/dl due to data and guidance of Brazilian Ministry of Health [5]. EPOR has many different reasons, faces and continues to be an everyday problem in the nephrology practice. Any national registry data reporting the ESA hyporesponsiveness are unavailable in Bulgaria and Europe too [6].

Material and Methods

A prospective study was conducted evaluating the serum erythropoietin and ferritin levels in Patients with CKD treated with dialysis within the scientific project №8/2024, funded by MU-Pleven and approved by the ethical committee of the same university. This type of study has not been made in Bulgaria before. The study carried out only ESRD patients total number of 100. A total of 88 patients treated with hemodialysis and 12 patients treated with peritoneal dialysis (CAPD) were included. An analysis was made of the correlations between the serum levels of endogenous erythropoietin, ferritin levels with haemoglobin doses of rHuEPO, serum creatinine, URR and main renal disease. The anti-erythrocyte antibodies were also examined. All patients in both RR methods were treated for RA with rHuEPO – Epoetin-beta, intravenous for HD and subcutaneous for the PD patients. All of HD group receiving intravenously iron after the HD seasons.

Experimental Samples

Every patient singed informed consent. An aseptic method was used to collect two samples of 2 and 5 ml of venous blood by usual punction. Other laboratory biochemical results were collected by monthly regular check-up of the patients in the dialysis unit.

Inclusion/Exclusion Criteria

There were inclusion and exclusion criteria: were selected 100 patients – 88 of them are on hemodialysis – both men and women with ESRD on HD therapy not less than 6 months on RRT with anemia, treated with ESA, vessel approach wasn't a minded. Other inclusion criteria were at least three months of poor or lack of ESA treatment response, elevated need of ESA dosing, low Hb levels under 110 g/l. In exclusion criteria section were Hb over 130 g/l, patients with tumors or other neoplastic formation, no recent hemotrasfusions or hematological conditions or immunosuppressive medications. All patients on CAPD were included.

Results

This study included 100 patients on dialysis, 88 are on HD treatment with renal anaemia Out of 88 people – 48 (54.6%) of them are males with mean age 60.7±13.7 years and 40 females (45.4%) with mean age 58.8±13.7 years. Both groups have non-significant difference in Hb levels for males mean 107.7±17.3 g/l, females – 106.7±12.4 g/l. Last 12 patients are treated with CAPD for at least six months of continuance both man and woman main age 49.5±14.3 years, Hb level 106.0±8.96 g/l. Levels of Hb CAPD group 106±11.3 g/l, iron – 10.2±2.9, ferritin levels 187.7±142.6 ng/m. Levels of endogenous erythropoietin – 20.6±14.4 U/l, not only normal but in most of these patients is elevated. Doses of ESA weekly 3500±2535.7 IU. The leading causes for CKD in that group are chronic glomerulonephritis, other main reasons are ADKPD, chronic pyelonephritis and diabetic nephropathy. All 100 patients on dialysis with renal anemia are receiving rHuEPO at the time of samples taking and iron also. In HD group 20 of 88 patients have low serum levels of endogenous erythropoietin – 3.6±0.9 U/l. This group is equally presented in both sex with mean age 57.8±11.6 years. This subgroup Hb levels is 110.9±11.7 g/l,

receiving Epoetin Beta mean weekly dose 5175±2970 IU, iron levels 12.4±4.8, ferritin levels 457.2±353.2 ng/ml. The leading causes for CKD are hypertensive nephropathy, chronic glomerulonephritis. Ischemic heart disease in 12 of them (60%), chronic heart failure in 8 (40%), chronic obstructive pulmonary disease in 6 (30%), diabetes mellitus in 4 (20%).

Rest of HD patients – 66 of them have normal levels of endogenous erythropoietin – 12.3±12.8 U/l. This group counts 30 women and 38 men with no significant difference in mean age – 60.7±12.04 and 60.4±14.5 years, respectively. Levels of Hb of whole group 106.2±16 g/l, iron – 20.1±17.4, ferritin levels 375±426.8 ng/m. Doses of ESA weekly 4631±3059.7 IU. The leading causes for CKD in that group are hypertensive nephropathy, chronic glomerulonephritis, other main reasons are ADKPD, chronic interstitial nephritis and diabetic nephropathy. Ischemic heart disease in 25 of them (36.7%), chronic heart failure in 18 (26.5%), chronic obstructive pulmonary disease in 11 (16.8%), diabetes mellitus in 22 (32.3%). In this group 60.3% of patients with CKD have started HD in emergency mode, they didn't know they had CKD and didn't make regular check-ups to their GP. HD and CAPD patients are compared in Table 1. The results show that in HD patients level of serum erythropoietin is much lower than in CAPD patients. But ferritin, weekly doses of ESA are on the contrary. There is no significant difference between Hb, iron levels in patients from both groups ($p<0.05$). It was noticed that patients with lower EPO are receiving higher doses of erythropoietin but low dose of iron weekly. CAPD patients are much younger. In patients treated with CAPD the level of serum erythropoietin varies between 4.7 and 45.5 U/l – none of them have low level. The average level of serum erythropoietin is significantly higher and the average age and duration of renal replacement therapy is significantly shorter compared to patients on HD ($p<0.05$).

Table 1

Group	Age	Hb	RBC	Hct	EPO level	Ferritin	ESA weekly dose	Fe
CAPD	49,5±15	106±11,3	3,1±0,3	0,35±0,06	20,6±14,4	187,7±142,6	3500±2535,7	10,2±2,9
HD	60,8±13,6	107,3±15,7	3,62±0,82	0,31±0,04	10,42±11,81	393,6±40,7	4382,35±3064,1	10,3±3,5

But when we compare result in CAPD, HD with EPO level and HD patients with high EPO levels in Table 2, we can conclude interesting tendency. CAPD patients are the youngest of the three groups, have the highest level of EPO and receive lowest doses of ESA weekly. The HD's with low EPO have higher Hb, Hct, ferritin and receive higher ESA than others. The HD's with high EPO are oldest and have the highest levels of serum iron. In all of the groups RBC hasn't significant difference. There aren't any sex differences in any of the groups. Of all HD patients group - 38 % have poor ESA response but in only 5 of them level of erythropoietin is low and none of them have iron deficit. The anti-erythrocyte antibodies were also examined, non of the patients have anti-erythrocyte antibodies. In any of studied patients haven't been found low level of serum albumin.

Table 2: Comparison of age, laboratory results between CAPD patients, HD patients with low EPO and HD patients with high EPO.

Group	Age	Hb	RBC	Hct	EPO level	Ferritin	ESA weekly dose	Fe
CAPD	49,5±15	106±11,3	3,1±0,3	0,35±0,06	20,6±14,4	187,7±142,6	3500±2535,7	10,2±2,9
HD low EPO	57,8±11,6	110,9±11,7	3,6±0,39	0,37±0,07	3,6±0,9	457,2±353,2	5175±2970	12,4±4,8
HD high EPO	60,5±13,5	106,2±16	3,5±0,4	0,32±0,08	12,3±12,8	375±426,8	4631,6±3059,7	20,1±17,4

Discussion

There are many papers and studies discussing different aspects for EPOR. There are a few studies with anti-erythrocyte antibodies in CKD patients on HD or CAPD. The most commented reasons discussed and observed for EPOR are iron deficiency, chronic inflammations, low albumin levels – nutrition status and other factors like – hyperparathyroidism, inadequate dialysis, ACE blockers.

Iron Deficiency

Iron deficiency is very common in CKD patients starting in early stages of CKD. ID is pointed to be the most reason for EPOR in CKD patients on dialysis therapy. This deficiency worsens the RA – causing constant fatigue, sleep problems, shortness of breath, shivering in the limbs, dark periorbital circles, sore muscles in the extremities. In HD population ID is more frequent because of chronic small blood loses during sessions. Ferritin mirrors the body's storage of iron, but due to inflammations isn't lowering, but the iron does first. Exactly the opposite ferritin could elevate in state of infections [2,5,6]. There are absolute of functional ID. Also inadequate iron food intake in CKD is usual especially if patients do not know for their CKD and anemia condition. Elevated alcohol consumption can provoke ID.

Chronic Infection or Inflammations

Second very important reason to develop EPOH is inflammation. Wu and Chinnadurai report that around 50% of CKD patients have elevated CRP and inflammatory markers even with no other signs of infection. They also point that the uremia activates pro-inflammatory cytokines reducing antioxidants, glutathione peroxidase [6,7]. Inflammation in uremic population could be chronic and usually associated with elevated mortality. In dialysis patient's catheters are risk factor for infections and chronic inflammations. Nikolovski, et al. [8] show the relation of EPOH and oxidative stress [8]. Further investigations are needed in episodes of dialysis catheter-associated infections.

Malnutrition

Patients with ESRD on HD not only in period of adaptation to the therapy, develop malnutrition. These patients suffer from nausea, vomiting, lack of appetite, causing low protein intake. All of this leads to muscle loss due to increased protein catabolism [2,9]. In malnutrition ferritin levels can also elevate. CKD patients need individual nutritional program and prescription, especially starting dialysis. The consideration of malnutrition, life and social status, protein energy waste are several aspects connected to CKD and can provoke EPOR.

Other Factors

Other factor like anti-erythropoietin antibodies, a hyperparathyroidism, inadequate dialysis, ACE blockers [2,6,10]. Mac Dougall, et al. [10] point that rHuEPO is well tolerated by most of the patients with CKD, a small number (in last 10 years even rarely) can format antibodies against endogenous erythropoietin, many described cases are for antibodies against epoetin Alfa [10]. In these cases, not only antibodies should be examined, a bone marrow examination too. ACE inhibitors ARB can provoke EPOR. Patients with malignancies, hematological conditions like multiple myeloma, leukemia, other systematic disease like amyloidosis. In this cases if patients are on dialysis usually due to regular check-ups and laboratory examinations this disease a more like to be found on time. Other authors conclude that obesity or just high BMI can too be risk factor for EPOR [8]. CKD-MBD is very often in CKD patients and starts almost at same time like anemia and worsens the anemia, CKD progression and quality of life. With advancing CKD PTH synthesis is constantly stimulated leading to hyperparathyroidism. The classical path of anemia is connected to hyperparathyroidism in dialysis population causing PTH hypersecretion. Next complication is a bone marrow fibrosis which slows EPO response and bone fractures, calcium composition in soft tissue. Inadequate dialysis can be other risk factor for EPOR. Santos, et al. [4] describes that the short timed dialysis sessions leading to poor depuration of uremic toxins and elevate EPOH. Meada et al conducted a study that prove that an hour to regular HD sessions can reduce the EPO weekly dose with 2000 UI [11,12].

- Our study didn't find ID in included patients.

Conclusion

EPOR is very often and complicated problem in CKD patients on dialysis. It affects not large number of patients. CKD patients usually are polymorbide, with late start of RRT. Our study shown that in PD group all of patients have normal levels of serum levels of endogenous erythropoietin. HD patients 38 % of all studied patients have poor ESA response but in only 5 of them level of erythropoietin is low without iron deficiency. Despite the recent studies there are many unknown risk factors and reasons for EPOH. It still stays the question: "Is there pure EPO insufficiency leading to RA in CKD patients on dialysis?". Many further investigation are needed. But it's very important to recognize the EPOR as early as possible, try to find the reasons and better the ESA response and correct the Hb to ameliorate quality of life of CKD population.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. MD Bethesda (2020) Unated States Renal Daat System: Anual data report: atlas of chronic kidney disease and end- stage renal disease in the United States. national institude of health, national institude of diabetes and digestive and kidney diseases.
2. Alves M T, Vilaça S S, Carvalho M d, Fernandes A P, Dusse L M, et al. (2015) Resistance of dialyzed patients to erythropoietin. Revista brasileira de hematologia e hemoterapia 37(3): 190-197.
3. Rabea Ahmed, Ragheb Ahmed, Kamal Ahmed M, Emara Mahmoud (2020) Predictors of erythropoietin hyporesponsiveness in chronic hemodialysis patients. Menoufia Medical Journal 33(1).
4. Santos E J F, Dias R S C, Lima J F B, Salgado Filho N, Miranda Dos Santos A (2020) Erythropoietin Resistance in Patients with Chronic Kidney Disease: Current Perspectives. International journal of nephrology and renovascular disease 13: 231-237.
5. Benkova Petrova M (2021) Factors responsible for the development of erythropoietin resistance among patients with chronic kidney disease undergoing dialysis. Journal of the Union of Scientists Varna Medicine and Ecology Series 2(26): 40-45.
6. Wu H H L, Chinnadurai R (2022) Erythropoietin-Stimulating Agent Hyporesponsiveness in Patients Living with Chronic Kidney Disease. Kidney diseases (Basel, Switzerland) 8(2): 103-114.
7. Hutchinson F N, Jones W J (1997) A cost-effectiveness analysis of anemia screening before erythropoietin in patients with end-stage renal disease. American journal of kidney diseases the official journal of the National Kidney Foundation 29(5): 651-657.

8. Nikolovski S, Medic Brkic B, Vujovic K S, Cirkovic I, Jovanovic N, et al. (2024) Severe Hyporesponsiveness to Erythropoiesis-Stimulating Agents in Patients on Chronic Hemodialysis-Reconsidering the Relationship with Thrombo-Inflammation and Oxidative Stress. Diagnostics (Basel, Switzerland) 14(21): 2406.

9. Gaweda A E, Goldsmith L J, Brier M E, Aronoff G R (2010) Iron, inflammation, dialysis adequacy, nutritional status, and hyperparathyroidism modify erythropoietic response. Clinical journal of the American Society of Nephrology CJASN 5(4): 576-581.

10. Macdougall I C, Roger S D, de Francisco A, Goldsmith D J, Schellekens H, et al. (2012) Antibody-mediated pure red cell aplasia in chronic kidney disease patients receiving erythropoiesis-stimulating agents: new insights. Kidney International 81(8): 727-732.

11. Maeda A, Tsuruya K, Maeda M, Yamasaki M, Nakashima A, et al. (2019) Hemodialysis treatment time versus erythropoietin dose requirement: Reduction in 2,000 units per week by extension of hemodialysis for 1 hour. Clinical nephrology 92(4): 174-179.

12. Farhad Sadia, u llah Inam, Kondaveeti Dr Suresh, SIDRA WALI, BUSHRA TAHREEM, et al. (2022) Detection of Anti-Erythropoietin Antibodies in Patients with Chronic Renal Failure Undergoing Hemodialysis. Pakistan Journal of Medical and Health Sciences 16(1).

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