Anemia of Patients on Hemodialysis During Treatment with Recombinant Erythropoietin

Tanja Boljevic¹,² and Damir Pelicic¹,²*

¹Clinical Center of Montenegro, Podgorica, Montenegro
²Faculty of Medicine, University of Montenegro, Podgorica, Montenegro
*Corresponding author: Damir Pelicic, Center for Science, Clinical Center of Montenegro, Podgorica, Montenegro

MINI REVIEW

Terminal kidney insufficiency is a condition of irreversible loss of kidney parenchyma what have for a consequence loss of kidney function. Before the replacement methods had been introduced (hemodialysis, peritoneal dialysis) patients with terminal insufficiency died [1,2]. Methods for kidney function replacement (RRT) are peritoneal dialysis and hemodialysis and kidney transplantation [3,4]. Hemodialysis is a method for kidney function replacement where blood is taking out extracorporeally. Taking the blood out of the body over acute blood vessels, two volume venous catheters or over punction of main blood vessels (AV fistula, AV graft) to the dialyser membrane is reached by use of highly sofisticated machines. Dialyser (membrane) is an artificial kidney which imitates glomerular basement membrane with selective permeability. Exchange of matter is performed through semipermeable membrane by simultan use of basic physical processes diffusion and osmossis. During process of the hemodialysis constant flow of the blood performs on one side of the membrane and from the other side dialyze liquid which has plasma like balance. However the basic bicarbonate hemodialysis that corrects the acidosis to the patient with 8,4 % of bicarbonate as well as derived modality HDF (hemodiafiltration) that allows depuration by ultrafiltration processes is still very far from the possibility of replacing the real kidney function. Diffusion and filtration processes provide controlled exchange of dissolved substances and water, remove some substances from the blood (urea, creatinine, natrium, water) and substitute necessary ones from the dialyse liquid (bicarbonate, calcium, magnesium) [5,6].

In this way it is posibble more or less successfully to replace (the excretory elimination of final products of protein decomposition, drugs) and partly regulatory function of the kidneys (composition and volume of extracellular fluid) while endocrine and metabolic function are day by day successfuly modulated and replaced by drugs (Erythropoietin, modulation of plasmarenin activity, influence on prostaglandin generation, substitution of active vitamine D3). Treating of the patients with hemodialysis in European countries started at the end of 50’s and beginning of

ARTICLE INFO

Received: November 06, 2020
Published: November 13, 2020

Citation: Tanja Boljevic, Damir Pelicic. Anemia of Patients on Hemodialysis During Treatment with Recombinant Erythropoietin. Biomed J Sci & Tech Res 31(5)-2020. BJSTR. MS.ID.005173.

Keywords: Anemia; Dialysis; Erythropoietin

ABSTRACT

Nowadays over million of patients with terminal kidney insufficiency are treated with some of the methods of the kidney function replacement. Appearance of the human recombinant Erythropoietin EPO approved by U.S. Food Administration 1989 , is one of the most significant progress in treating patients. Three of the pathophysiological processes are involved in the appearance of anemia in the chronic kidney insufficiency : insufficient production of erythropoietin and decreased response of stem cells of the erythrocytopoiesis in the bone marrow to action of Erythropoietin (EPO); inhibition of the bone marrow with toxic meatabolites that are not eliminated from the body due to disturbed excretory kidney function; uremic toxins acts as inhibitors of heme synthesis but may have an inhibitory effect to erythroid stem cell differentiation. The aim of this work was to show the role of Erythropoietin to the patients on hemodialysis.

Abbreviations: ERA: European Renal Association; EDTA: European Dialysis and Transplant Association; NKF: National foundation for kidney; EBPG :European Best Practice Guide-line; DOQI: Dialysis Outcomes quality Initiative
In patients with chronic kidney insufficiency, normocytic and normochromic anemia are regular present what significantly contributes to the symptomatology of chronic kidney failure. It is usually observed when JGF value falls between 30ml / min and creatinine rises to about 265um / l. The hematocrit progressively decreases below 15-20 % in the absence of bleeding. The severity of anemia usually corresponds to the degree of azotemia. When anemia to the patients with chronic kidney insufficiency is not treated properly it includes a wide range of psychological disorders that include decreased tissue oxygenation, decreased delivery of oxygen to the tissues and their utilization. Erythropoiesis is suppressed by the effects of retained toxins on erythrocytes, reducing biosynthesis of erythropoietin in diseased kidneys such as with the presence of circulating inhibitors of erythropoiesis [11,12]. Many factors contributing to anemia [13] and they are hypersplenism, gastrointestinal bleeding, chronic blood loss during hemodialysis, anticoagulant therapy also during hemodialysis and toxic effects of aluminium. Anemia in a state of chronic kidney insufficiency is caused by three pathophysiological mechanisms, insufficient production of erythropoietin, reduced response of selected erythrocytopoiesis stemm cells in the bone marrow to the action of erythropoietin (EPO); inhibition of bone marrow by toxic metabolites that are not eliminated from the body due to impaired excretory kidney function, uremic toxins act as inhibitors of heme synthesis but may have an inhibitory effect on erythroid stem cell differentiation. It is considered that pharathormone, which is secreted in chronic kidney insufficiency is one of the inhibitors of erythrocytopoiesis, the shortened life of erythrocytes is a consequence of metabolic products that act as extracorpuscular hemolytic factors.

The development of anemia leads to attempts of involving compensatory mechanisms such as increased erythropoiesis but this is impossible due to lack of EPO producing cells, increased ventilation but shortness of breath because of the saturation of the respiratory system, acceleration of circulation which includes increased possibility for a stoke and cardiac output. Clinical manifestation of anemia are [13] weakness, intermittent claudication, heart failure and sometimes angina pectoris. The clinical picture is dominated by various symptoms and signs of kidney insufficiency while palor of the skin and visible mucous membranes indicate anemia. The diagnosis of anemia is set by examination of the peripheral blood and bone marrow with signs of the presence of chronic kidney or renal failure. Peripheral blood anemia is normocytic and normochromic, there is rarely macrocytosis or hypochromacy and microcytosis, reticulocyte count is normal or slightly reduced, platelet function is impaired, which causes a tendency to bleed, in the peripheral blood smear erythrocytes are observed, bone marrowcellularity is usually normal, which is in relation to the degree of anemia as a pathological finding where erythroid hyperplasia would be expected.

In treatment good results are achieved by application of recombinant human Erythropoietin [14] which is efficient and well tolerated in attempt to achieve and sustain concetration of Hb with it from 100 -120 g/l. When the target concretation is reached the dose of EPO should be reduced [4,15-17]. Kidney transplation represents one successful way of anemia treatment in chronic kidney insufficiency [4]. Multi-centric studies show results of the therapy with Erythropoietin in anemia suppression to the patients with chronic kidney failure. Improving that Erythropoietin is the most significant factor for anemia [18-21]. The basic reason of anemia to the patients with chronic kidney failure is insufficient production of Erythropoietin in the kidneys [22]. Erythropoietin is a hormone, sialoglycoprilen, essential for the final differentiation of stem cells of erythropoiesis. It is synthesised mostly in kidneys, ports in circulation and in the serum of the health patients there is 20mm/ml. Synthesis of EPO is regulated by the mechanism of negative feedback and it depends of it how the tissues are supplied by the oxygen. Beside kidneys in EPO synthesis are partly involved extrarenal sources, the most probably liver in which Epo is formed exclusively in the fetus. In an adult a kidney is an organ in which Epo is already formed and the liver is responsible for synthesis around 20 % of EPO while hypoxia stimulates synthesis of EPO but not already synthesised EPO which is deposited in the kidney. EPO is produced by highly differentiated cells of connective tissue, fibroblasts placed in the renal cortex between renal tubula. In these cells there isn't depo of Erythropoietin because the whole amount is delivered after the synthesis.

The strongest stimuli of EPO synthesis is hipoxia. It brings to the production of EPO- MRNA in the mentioned cells. It is considered that a definite role in this process belongs to the renal tubula. During the process of fibrosis development due to renal failure it appears massive fibroblast proliferation in the renal cortex. Progressive
loss of tubula cause loss of links between EPO productive cells and tubula that surrounds them. Fibroblast changes their phenotype and became miofibroblast and loose ability of production EPO. As a consequence of that appears sharp fall of EPO in the blood. Before 1989 characteristic lack of Erythropoietin in renal failure could be treated only with blood transfusion and anabolic steroids with limited success and following complications. Appearance of the recombinant human Erythropoietin, EPO improved by US Food and Drug Administration in 1989 is one of the most significant progress in the treatment of kidney patients in the last decade. Studies which follow the level of mortality and hospitalization support criteria of National Kidney Foundation Dialysis Outcomes quality Initiative (DOQI) that hematocrit in range from 33 to 36 % provides the best following effects [23].

EPO could be given intravenously or subcutaneously. The most of the studies show that application of EPO subcutaneously has saving effects [24,25] where optimal value of hematocrit is achieved with smaller costs EPO [20]. There are studies which talk about advantages of subcutaneously implementation of Erythropoietin [26-30] in the therapy of anemia to these patients in relation to venous application and they are lower doses and level of pain and costs of the treatment. Efficiency of EPO therapy depends of adequate dose, frequency and application. It is common to be given a dose of 20-50IU / kg TM three times a week and then if a target hematocrit isn’t reached to increase dose to 25-96% every fourth week [31]. If it is necessary to apply bigger dose than 150 UI /kg three times a week than it is considered that exists resitency to EPO. Therapy guideline : Supression of anemia in HBI by giving of Erythropoietin Sc 80-120IU /kg a week (is divided in 2-3 doses a week) IV -120-180IU/kg a week(divided into 3 doses a week) target Hct / Hb 33-36 %, 11-12g/dl optimal way of correction. Increment of Hct for 4-6 % during 4 weeks (achievement of target value inside 2-3 months period). Occasional single values of hemoglobin that are above or under wished ones could be noticed to the patients because of the variability. Variability of hemoglobin should be treated thorough adoption of the dose of target range of 10g/dl (6,2mmol) up to 12g/dl (7,5mmol/l) [32,33]. Keeping the level of hemoglobin above 12g/dl (7.5mmol/l) should be avoided. If the speed of hemoglobin rise is bigger than 2g/dl (1.25mmol/l ) during one month or it rises to 12g/dl (7.45mmol/l) ja dose should be lower for 25%. If the level of hemoglobin continues to rise therapy should be stopped until its level starts to fall and then begin the therapy again in a dose for 25 % lower than the previous one. Patients condition should be followed carefully to provide application of the lowest dose of Erythropoietin that provides adequate control of anemia symtoms. If the hypertension is present or some other cardiovascular or cerebrovascular disease or disease of the periferal blood vessels level of the Hb should be decided according to the health condition of the patient.

References
1. Djukanovic L, Radovic M (2002) Epidemiology of end-stage renal disease and current status of hemodialysis. Int J Artif Organs 25(9): 852-859.  
2. Fernandez JM, Carbonell ME, Mazzuci N, Petruccelli D (1992) Simultaneous analysis of mortality and morbidity factors in chronic hemodialysis patients. Kidney Int 41(4): 1029-1034.  
3. Greaves SC, Gamble GD, Collins JF, G A Whalley, D N Sharpe (1994) Determinant of left ventricular hypertrophy and systolic dysfunction in chronic renal failure. Am J Kid Dis 24(5): 768-776.  
4. Grzeszczak W, ladyslaw Sulowicz, Boleslaw Rutkowski, Amedeo F de Vecchi, Renzo Scansanz, et al. (2005) Nephrol Dial transplant 20: 936-944.  
5. Kerr PG (2006) Renal anaemia : recent developments , innovative approaches and future directions for improved management Nephrology ( Carlton ) 11 (6): 542- 548.  
6. Lazarus JM, Bradley MD, William FO (1996) Haemodialysis . In: Brenner MB and rector FC (9th Edn.) (Eds.), The Kidney W. B. Saunders, USA : 2425-2506.  
7. Locatelli F, Pedro Alijama, Peter Bárány, Bernard Canaud, Fernando Carrera, et al. (2004) Revised European best practice guidelines for the management of anemia in patients with chronic renal failure. Nephrol Dial transplant 19 ( Suppl 2 ) : 1 -47.  
8. Lebdo I, Kessler M, Wim nav Biesen, Wanner C, Wieck A, et al. (2001) Initiation of dialysis-options from an international survey: Report on the Dialysis Opinion Symposium at the ERA-EDTA Congress, 18 September 2000, Nice, Nephrol Dial transplant 16(6): 1132-1138.  
9. Ratković M (2002) Procjena kvaliteta liječenja bolesnika sa terminalnom bubrenzom insuficijencijom hemodijalizma. Doktorska disertacija, Med fak Univ Beograd.  
10. Stosevic M (2002) Uporedna analiza indeksa adekvatnosti dijalize upotrebljavanih kliničkih parametara pri raznim nivoima dijaliziranosti kod bubrežnih bolesnika na hemodijalizi. Doktorska disertacija, Med fak Univ Beograd, 2002.  
11. Albertazzi A, Battistel V , Libertato L (1998) Efficacy and tolerability of recombinant treatment in pre-dialysis patients: Results of a multicenter study. Int J Organs 21(1): 12-18.  
12. KDOQI (2006) Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. Am J Kidney Dis 47 ( 5 Suppl3 ) : 16-85.  
13. Lacson E, Norma Ofsthun, J Michael Lazarus (2003) Effect of variability in anemia management on haemoglobin outcomes in ESRD. Am J Kidney Dis 41(1): 111-124.  
14. (2001) NKF-K/DOQI Clinical practice guidelines for anemia of chronic kidney disease Am J Kidney Dis 37: 182-238.  
15. Besarab A, Amin N, Ahsan M (2000) Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. J Am Soc Nephrol 11(3): 550-558.  
16. Besarab A (2000) Physiological and pharmacodynamic considerations for route of EPO administration. Semin Nephrol 20(4): 364-374.  
17. Weinreich T , Robert A Mantier, Thomas Weinreich, Armin W Scherhag, GAIN Investigators (2007) Effectiveness and safety of haemoglobin management with epoetin beta GAIN final results. Word Congress of Nephrology, Rio de Janeiro, Brazil 25(4):961-70.  
18. Chuichi S, Terno S, Moriham M (1992) Serum Erythropoietin Concentrations and Iron status in Patients on chronic haemodialysis. Clinical chemistry 38(2): 199-203.  
19. Lopez Gomez J, Portoles J, Alijama P (2008) Factors that condition the response to erythropoietin in patients on hemodialysis and their relation
to mortality. Service of Nephrology, Hospital Universitario Gregorio Maranon, Madrid, Spain. Kidney International 74 Suppl (111): 75-81.

20. Onyekachi I, Feldman J, Eli A Friedman (1996) The intensity of hemodialysis and response to erythropoietin in patients with end-stage renal disease. The new England Journal of medicine 334: 420-425.

21. Taylor J, Belch J, McLarm M (1993) Effect of Erythropoietin therapy and with drawal on blood coagulation and fibrinolysis in hemodialysis patients. Renal Unit and Department of Medicine, Scotland, United Kingdom. Kidney International 44: 182-190.

22. Rath T (2007) Reaching the target today. Presented at Rio de Janeiro, Brazil.

23. Mimnn A (1992) Renal effects of antihypertensive agents in parenchimal renal disease and renovascular hypertension. J Cardiovasc Pharmacol 19(6): 45-50.

24. Patterson P, Allon M (1988) Prospective evaluation of an anemia treatment algorithm in hemodialysis patients. Am J Kidney Dis 32(4) : 635-641.

25. Weiss IG, Naomi Clyne, Jose Divino Filhio, Carsten Frisenette Fich, Jan Kurkus, et al. (2000) The efficacy of once weekly compared with two or three times weekly subcutaneous epoetin beta. Results from a randomized controlled multicentre trial. Swedish Study Group. Nephrol Dial Transplant 15(12) : 2014-2019.

26. Locatelli F, Andrulli S, Memoli B, Camilla Maffei, Lucia Del Vecchio, et al. (2006) Nutritional-inflammation status and resistance to erythropoietin therapy in haemodialysis patients. Nephrol Dial Transplant 21(4): 991-998.

27. Besarb A, Carolina Reyes, John Hornberger (2002) Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in haemodialysis patients. Am J Kidney Dis 40(3): 439-446.

28. Goldsmith D, O Donoghue D (2005) Optimizing hemoglobin control with erythropoiesis-stimulating agent: results of the Subcutaneous Erythropoietin Control (SEC) study. Presented at ASN Philadelphia, USA.

29. Grzeszczak W (2002) Once weekly and once fortnightly (every two weeks) subcutaneous epoetin beta is effective in patients with chronic renal anaemia. Oral presentation at the 39th Congress of the ERA-EDTA, 14-17 July 2002, Copenhagen, Denmark.

30. Locatelli F, Conrad A Baldamus, Giuseppe Villa, Alexandru Ganea, Angel L Martin de Francisco (2002) Once-weekly compared with three times-weekly subcutaneous epoetin β : Results from a randomized, multicenter, therapeutic equivalence study. Am J Kidney Dis 40(1): 119-125.

31. Weiss L (2001) Flexible dosing schemes for recombinant human erythropoietin—lessons from our daily practice. Nephrol Dial Transplant 16(7): 15-19.

32. Gilbertson D (2006) The effect of hemoglobin variability on hospitalization and mortality. Presented at EDTA, Glasgow, UK.

33. Ebben JP, David T Gilbertson, Robert N Foley, Allan J Collins (2006) Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. Clin J Am Soc Nephrol 1(6): 1205-1210.

ISSN: 2574-1241
DOI: 10.26717/BJSTR.2020.31.005173

Damir Pelicic. Biomed J Sci & Tech Res

This work is licensed under Creative Commons Attribution 4.0 License
Submission Link: https://biomedres.us/submit-manuscript.php

Assets of Publishing with us
- Global archiving of articles
- Immediate, unrestricted online access
- Rigorous Peer Review Process
- Authors Retain Copyrights
- Unique DOI for all articles

https://biomedres.us/