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Anemia of Patients on Hemiodialysis During Treatment with Recombinant Erythropoietin

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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 erythropoetin 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 ihibitory 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 Trasplant Association; NKF: National foundation for kidney; EBPG :European Best Practice Guideline; DOQI: Dialysis Outcomes quality Initiative

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Terminal kidney insufficiency is a condition of irreversible loss of kidney parenchyma what have for a consequence loss of kidney function. Before the replecement methods had been introducted (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 fuction 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 dialyzer membrane is reached by use of highly sofisticated machines. Dialyzer (membrane) is an artifical 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 disolved 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 successfuly 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

60's and doctors who started application of these methods found in 1964 Association for dialysis and transplant (European Dialysis and Trasplant Association- EDTA) [7] AND Europen Register got the name ERA – EDTA (European Renal Association) [8]. Treatment by hemodialysis in Montenegro started on 18 June in 1979 in the Centre for hemodialysis in Podgorica and from 1989 exsist seven centers where around 170 patients have a treatment and every year around 50 new patients demand tretment by hemodialysis. By hemodialysis provides better life quality of these patients [9]. National foundation for kidney in The USA (NKF) I EBPG (European Best Practice Guideline) published a couple of the recomendations , such as recomendation for adequacy of hemodialysis (dose of hemodialysis) [10]. Measurement of the realised hemodialysis dose is usualy counted by counting of the index Kt/ W. Kt/V what is a measure of plasma amount purified from urea , divided with volume of distribution for urea. It is widely accepted attitude that the patien is properly dialised when Kt /V is between 1,2 i 1,5 .

Anemia

In patients with chronic kidney insufficiency , normocytic and normochromic anemia are regulary present what singnificantly 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 hematrocrit 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 psyhological disorders that include decreased tissue oxygenation, decreased delivery of oxygen to the tissues and their utilization. Erythropoiesis is supressed 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 metabolits that are not eliminated from the body due to imparied excretory kidney function, uremic toxins act as inhibitors of heme syntesis 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 ia a consequence of metabolic products that act as extracorpuscular hemolytic factors.

The development of anemia leeds 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 hypochromia and microcytosis, reticulocyte count is normal or slightly reduced, platelet function is imparied, which causes a tendency to bleed, in the peripheral blood smear erythrocytes are observed , bone marrpw cellularity 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 efficent 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 transplatation represents one succesful way of anemia treatment in chronical kidney insufficiency [4]. Multucentric 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 differentation of stem cells of erythropotesis. 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 stimulies synthesis of EPO but not already synthesised EPO which is deposited in the kidney. EPO is produced by highly differented cells of connective tissue, fibrolasts 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 synhesis 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 tibula. During the process of fibrosis development due to renal failure it appears massive fibroblast proliferation in the renal cortex. Progressive

loss of tibula cause loss of links between EPO productive cells and tubula that surroundes 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 stereoids 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 optinal value of hematocrit is achieved with smaller losts 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 wekk than it is considered that exsists resistency to EPO. Therapy guideline : Supression of anemia in HBI by giving of Erythropoietin Sc 80-120J /kg a week (is divided in 2-3 doses a week) IV -120-180J/kg a week (divided into 3 doses a week) target Hct / Hb 33-36 % , 11-12g/dl optimal way of correction. Increasment of Hct for 4-6 % during 4 weeks (achievement of target value inside 2-3 months period). Ocassional 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 throuh adoption of the dose of target range of 10g/dl (6,2mml) 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)a 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 Eritropoetin that provides adequate control of anemia symtoms. If the hypertension is present or some other cardiovascular or cerebrovascular disesase or disease of the periferal blood vessels level of the Hb should be decided according to the health condition of the patient.

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