ORIGINALNI RAD

UDK BROJEVI:
616.155.194-085 616.
61-78-06
DOI: https://www.doi.org/10.5937/zdravzast51-40170

FAKTORI KOJI DOPRINOSE BOLJEM OPORAVKU OD ANEMIJE OSOBAMA NA HEMODIJALIZI PRILIKOM PRIMENE REKOMBINANTNOG ERITROPOETINA

Tanja Boljević[1], Damir Peličić [1*]

[1] Klinički centar Crne Gore, Medicinski fakultet, Univerzitet Crne Gore, Podgorica, Crna Gora

[*] Korespondencija: [*] Damir Peličić, Centar za Nauku, Klinički centar Crne Gore, Crna Ljubljanska bb, Podgorica 20000; e-mail: damir.pelicic@kccg.me

SAŽETAK

Uvod/Cilj: Anemija se najčešće javlja kod bolesnika na hroničnom programu hemodijalize i uzrok je smanjenog kvaliteta života. Cilj studije je bio da identifikuje faktore koji doprinose osobama na hemodijalizi bolju kontrolu anemije primenom rekombinantnog eritropoetina.
Metod: Studijom preseka su 2017. godine, bile obuhvaćene 52 osobe na hemodijalizi iz Kliničkog centra Crne Gore. Ispitanicu su podeljini na one kod kojih je posle 3 meseca od primene rekombinantnog eritropoetina došlo do porasta hemoglobina na zadovoljavajuće vrednosti (110 g/l ili više) (grupa 1) i one kod kojih je vrednost hemoglobina i dalje bila niža od 110 g/l (grupa 2). Od svih ispitanika prikupljeni su podaci iz istorija bolesti. U statističkoj analizi podataka korišćen je t-test.
Rezultati: Posle tromesečne primene terapije eritropoetinom samo kod 21 bolesnika (40,4%) je postignuta ciljna vrednost hemoglobina od 110 g/l ili više (grupa 1), a kod 59,6% vrednosti hemoglobina su bile niže od 110 g/l. Ispitanici kod kojih nisu postignute ciljne vrednosti hemoglobina su primali značajno veće prosečne doze eritropoetina i imali veći indeks telesne mase nego ispitanici kod kojih su postignute ciljne vrednosti hemoglobina. Između ispitivanih grupa nije bilo značajne razlike u odnosu na odgovor na eritropoetin, dužinu trajanja terapije eritropoetinom, dužinu trajanja dijalize, starost ispitanika, debljinu kožnog nabora, obim nadlaktice, vrednosti transferina, broj eritrocit, vrednosti albumina, hemoglobina, hamatokrita i gvožđja.
Zaključak: Mogući faktori koji doprinose lošijoj kontroli anemije su više doze eritropoetina i veći stepen uhranjenosti procenjen prema indeksu telesne mase. Neophodna su dalja istraživanja u cilju pronalaženja faktora koji bi doprineli odklanjanju anemije kod osoba na hemodijalizi, jer nelečena anemija može dovesti do brojnih nepovoljnih ishoda (loš kvalitet života, kardiovaskularne bolesti, cerebrovaskularni insult, smanjenje opšte stope preživljavanja i drugo).

Ključne reči: hemodijaliza, eritropoetin, hronična bubrežna insuficijencija

Uvod

Anemija se definiše kao koncentracija hemoglobina u krvi manja od 120 g/l kod žena i manja od 130 g/l kod muškaraca (1). Ona je prateća pojava kod bolesnika na hroničnom programu hemodijalize i uzrok je smanjenog kvaliteta života. Multicentrične studije sprovedene na osobama sa hroničnom bubrežnom insuficijencijom (HBI) su pokazale da je nedostatak eritropoetina ključni faktor za nastanak anemije kod ovih osoba (2-7).

Većina studija pokazuje da primena eritropoetina supkutano ima „štedeći efekat" (8,9), pri čemu se optimalna vrednost hematokrita postiže manjim dozama eritropoetina (10). Postoji više studija koje govore o prednosti supkutane u odnosu na intravensku primenu eritropoetina u terapiji anemije kod ovih bolesnika, a to su: smanjenje potrebne doze eritropoetina, manji bol pri aplikovanju koji opisuju bolesnici, i smanjenje troškova lečenja (11,12). Efikasnost terapije eritropoetinom zavisi od adekvatne doze, učestalosti primene i načina davanja. Uobičajeno je da se daje u dozi 20-50 IJ/kg telesne mase, tri puta nedeljno, a zatim, uko-

ORIGINAL PAPER

UDK NUMBERS:
616.155.194-085 616.
61-78-06
DOI: https://www.doi.org/10.5937/zdravzast51-40170

FACTORS CONTRIBUTING TO THE RECOVERY FROM ANEMIA IN HEMODIALYSIS PATIENTS DURING THE ADMINISTRATION OF RECOMBITANT ERYTHROPOIETIN

Tanja Boljevic[1], Damir Pelicic [1*]

[1] Clinical Center of Montenegro, Faculty of Medicine, University of Montenegro, Podgorica, Montenegro

[*] Correspondence: [*] Damir Pelicic, Center for Science, Clinical Center of Montenegro, Podgorica, Montenegro, Ljubljanska bb, Podgorica 20000, Montenegro; e-mail: damir.pelicic@kccg.me

SUMMARY

Introduction/Aim: Anemia is the commonest complication in patients on a chronic hemodialysis program and is the cause of reduced quality of life. The aim of this study was to identify the factors that contribute to the better control of anemia with the help of recombinant erythropoietin in persons undergoing hemodialysis.
Methods: The cross-sectional study was conducted in 2017 and it included 52 persons on hemodialysis at the Clinical Center of Montenegro. The participants were divided into those, in whom hemoglobin values increased to satisfactory values (110 g/l or more) after three months of application of recombinant erythropoietin (group 1), and those, in whom hemoglobin values were lower than 110 g/l (group 2). Data were collected from the medical history of all participants. T-test was used for the statistical analysis of data.
Results: After the three-month administration of erythropoietin, the target value of hemoglobin of 110 g/l or more (group 1) was achieved in only 21 patients (40.4%), while hemoglobin values were below 110 g/l in 59.6% of patients. Participants, in whom target values of hemoglobin were not achieved, received significantly higher average doses of erythropoietin and they had higher body mass index in comparison to participants, in whom the target values were achieved. There was no significant difference between the examined groups regarding the response to erythropoietin, duration of erythropoietin therapy, duration of hemodialysis, participants' age, skin-fold thickness, upper arm width, transferrin values, number of erythrocytes, value of albumin, hemoglobin, hematocrit and iron.
Conclusion: Possible factors that contribute to worse control of anemia are higher doses of erythropoietin and greater level of nutritional status estimated according to the body mass index. Further research is necessary aimed at finding factors that would contribute to the elimination of anemia in persons on hemodialysis, because non-treated anemia may lead to numerous unfavorable outcomes (poor quality of life, cardiovascular diseases, cerebrovascular insult, decreased survival rate etc.).

Key words: hemodialysis, erythropoietin, chronic kidney insufficiency

Introduction

Anemia is defined as the concentration of hemoglobin lower than 120 g/l in women and lower than 130 g/l in men (1). It is the accompanying complication in patients on a chronic hemodialysis program and it is the cause of the poor quality of life. Multicentric studies that included persons with chronic kidney insufficiency have shown that the lack of erythropoietin is a key factor for the development of anemia in these persons (2-7).

Most studies have shown that the subcutaneous administration of erythropoietin has a "saving effect" (8,9), while the optimal value of hematocrit is achieved with smaller doses of erythropoietin (10). There are several studies that speak about the advantages of subcutaneous application of erythropoietin in comparison to intravenous application in the treatment of anemia in these patients, and they include the following: reduction of the necessary dose of erythropoietin, less painful injection described by patients, and reduced costs of treatment (11,12). The efficacy of treatment with erythropoietin

liko nije dostignut ciljni hematokrit, svake četvrte nedelje doza se povećava za 25-96% (13). Ukoliko su potrebne doze veće od 150 IJ/kg telesne mase, tri puta nedjeljno, smatra se da postoji rezistencija prema eritropoetinu.

Prema terapijskom vodiču (14), za korekciju anemije kod HBI neophodno je davanje eritropoetina supkutano u dozi 80-120 IJ/kg telesne težine nedeljno (podeljeno u 2-3 doze) ili intravenski 120-180 IJ/kg telesne težine nedeljno (podeljeno u 3 doze). Ciljna vrednost hematokriat treba da bude od 33 do 36%, a hemoglobina od 11 do 12 g/dl. Optimalni način korekcije podrazumeva porast vrednosti hematokrita za 4-6% tokom 4 nedelje (a ciljne vrednosti unutar 2-3 meseca). Varijabilnost vrednosti hemoglobina treba tretirati kroz prilagođavanje doze, imajući u vidu ciljni opseg hemoglobina od 10g/dl (6,2 mmol/l) do 12 g/dl (7,5 mmol/l) (16). „Održavanje nivoa hemoglobina iznad 12g/dl (7,5 mmol/l) treba izbegavati (14). Ako je brzina porasta hemoglobina veća od 2g/dl (1,25 mmol/l) tokom jednog meseca ili se rastući nivo hemoglobina približava 12g/dl (7,45 mmol/l), dozu treba smanjiti za 25%. Ukoliko nivo hemoglobina nastavlja da raste, terapiju treba prekinuti dok nivo hemoglobina ne počne da opada, kada terapiju treba ponovo započeti u dozi koja je 25% niža od prethodno primenjene doze."

Terapija eritropoetinom se deli u dve faze: faza korekcije i faza održavanja. U fazi korekcije vrši se supkutana primena eritropoetina (15). „Inicijalna doza je 3 × 20 IJ/kg telesne težine nedeljno. Ova doza se može povećavati svake 4 nedelje za 3 × 20 IJ/kg telesne težine nedeljno, ako povećanje hemoglobina nije adekvatno (< 0,25 g/dl nedeljno). Ova nedeljna doza se može podeliti u dnevne doze. Maksimalna doza ne sme da pređe 720 IJ/kg telesne težine nedeljno. U fazi održavanja da bi se hemoglobin održao na nivou između 10 i 12 g/dl, doziranje se inicijalno smanjuje na polovinu prethodno date doze. Posle toga se doza podešava u intervalima od jedne do dve nedelje individualno za svakog bolesnika (doza održavanja) (13)."

Terapija eritropoetinom je uobičajeno dugoročna terapija. Podaci o šemi doziranja jednom nedeljno zasnivaju se na kliničkim ispitivanjima sa trajanjem terapije od 24 nedelje (16). U kliničkim ispitivanjima (17) primećen je povećan rizik od smrti i ozbiljnih kardiovaskularnih događaja kada je ciljna vrednost hemoglobina, postignuta lekovima za stimulaciju eritropoeze, bila viša od 12 g/dl (7,5 mmol/l). Kontrolisana klinička ispitivanja nisu pokazala značajne koristi koje bi se mogle pripisati primeni eritropoetina, kada se koncentracija hemoglobina poveća iznad nivoa neophodnog za kontrolu simptoma anemije i izbegavanje transfuzije krvi (18-20).

Na osnovu rezultata kliničkih ispitivanja kojima je obuhvaćeno 1725 pacijenata, očekuje se da približno 8% pacijenata koji se leče eritropoetinom ima neka neželjena dejstva (21). Najčešće neželjeno dejstvo tokom terapije eritropoetinom jeste povećanje krvnog pritiska i pogoršanje već postojeće hipertenzije (5). Terapija eritropoetinom se vrlo dobro podnosi, kako subjektivno, tako i objektivno i ima bezbroj prednosti u odnosu na transfuzije krvi, čija primena može biti praćena brojnim neželjenim reakcijama.

Cilj ove studije preseka je bio da se identifikuju faktori koji kod osoba na hemodijalizi tokom primene rekombinantnog eritropoetina doprinose njihovom boljem oporavku od anemije.

Metod

Ovom studijom preseka obuhvaćene su 52 osobe na hemodijalizi koje su bile hospitalizovane na Klinici za urologiju i Klinici za nefrologiju, Kliničkog centra Crne Gore. Svi ispitanici su primali humani rekombinantni eritropoetin tokom poslednja 3 meseca. Ispitanici su podeljeni u dve grupe na osnovu odgovora anemije na primenu eritropoetina tokom poslednja 3 meseca. Prvu grupu činile su osobe na hemodijalizi sa postignutim ciljnim hemoglobinom od 110 g/l ili više (grupa 1), a drugu grupu osobe na hemodijalizi sa ciljnim hemoglobinom nižim od 110 g/l (grupa 2). Od svih ispitanika prikupljeni su podaci iz istorija bolesti. Za sve ispitanike prikupljeni su podaci koji se odnose na uzrast, dužinu trajanja hemodijalize, dužinu primene eritropoetina, doza eritropoetina, odgovor na dozu eritropoetina, vrednosti eritrocita, hematokrita i albumina. Istraživanje je odobreno od strane etičkog komiteta Kliničkog centra Crne Gore. U statističkoj analizi podataka korišćen je Studentov t-test.

Rezultati

Studija preseka je obuhvatila 52 osobe koje su na hemodijalizi i koje su lečene od anemije primenom eritropoetina (tabela 1). Posle primene terapije eritropoetinom samo kod 21 bolesnika (40,4%)

depends on the adequate dose, the frequency of administration and manner of administration. It is usually administered in a dose 20-50 IU/kg of body weight, three times a week, and then, if the target hematocrit is not achieved, every fourth week the dose is increased for 25-96% (13). If the necessary doses are higher than 150 IU/kg, three times a week, it is deemed that it is the resistance to erythropoietin.

According to the treatment protocol (14), in order to treat anemia in chronic kidney insufficiency, erythropoietin should be administered subcutaneously in a dose 80-120 IU/kg (divided into 2-3 doses) or intravenously 120-180 IU/kg a week (divided into 3 doses). Target values of hematocrit should be 33-36%, and of hemoglobin 11-12 g/dl. The optimal correction means the increase in hematocrit values for 4-6% during 4 weeks (while target values within 2-3 months). The variability of hemoglobin values should be treated through dose adjustment, considering the target range of hemoglobin from 10g/dl (6.2 mmol/l) to 12 g/dl (7.5 mmol/l) (16). "The maintenance of hemoglobin level above 12g/dl (7.5 mmol/l) should be avoided (14). If hemoglobin value rises more than 2g/dl (1.25 mmol/l) within one month or the increasing hemoglobin reaches 12 g/dl (7.45 mmol/l), a dose should be reduced for 25%. If the level of hemoglobin continues to increase, the therapy should be interrupted until the hemoglobin level begins to decrease, and then the therapy should be reintroduced in a dose which is 25% lower than the previously administered dose."

The treatment with erythropoietin is divided into two phases: the correction phase and maintenance phase. In the correction phase, erythropoietin is administered subcutaneously (15). "The initial dose is 3 × 20 IU/kg per week. This dose may be increased every fourth week for 3 × 20 IU/kg per week if the hemoglobin increase is not adequate (< 0.25 g/dl a week). This weekly dose may be divided into daily doses. Maximal dose must not exceed 720 IU/kg per week. In the maintenance phase, in order to keep hemoglobin at the level between 10 and 12 g/dl, the dose is initially reduced to one half of the previously administered dose. After that, the dose is adjusted within one to two weeks individually for each patient (maintenance dose) (13)."

The erythropoietin treatment is usually a long-term treatment. Data on the scheme of doses once a week are based on the clinical trials in which therapy lasts 24 weeks (16). In the clinical trials (17), it was noticed that the risk of mortality and severe cardiovascular events increased when the target value of hemoglobin, which was achieved with the help of medications that stimulate erythropoiesis, was higher than 12 g/dl (7.5 mmol.l). Controlled clinical trials did not show significant benefits that could be attributed to the use of erythropoietin, when the concentration of hemoglobin increased above the level necessary for the control of the symptoms of anemia and avoidance of blood transfusion (18-20).

According to the results of clinical trials, which included 1725 patients, it is expected that approximately 8% of patients who are treated with erythropoietin will have some side effects (21). The most common side effect during the erythropoietin treatment is the elevation of blood pressure and worsening of already existing hypertension (5). The treatment with erythropoietin is well-tolerated, subjectively and objectively, and it has numerous advantages in comparison to blood transfusion, whose application may be accompanied by numerous side effects.

The aim of this study was to identify factors that contribute to the better recovery from anemia in patients on hemodialysis during the administration of recombinant erythropoietin.

Method

This cross-sectional study included 52 patients on hemodialysis, who were hospitalized at the Clinic of Urology and Clinic of Nephrology at the Clinical Center of Montenegro. All participants received human recombinant erythropoietin during the previous three months. The participants were divided into two groups according to their response to the application of erythropoietin during the last three months. The first group included persons on hemodialysis with the achieved target hemoglobin of 110 g/l or higher (group 1), while the second group included persons on hemodialysis with the target hemoglobin lower than 110 g/l (group 2). Data were collected from the medical history of all participants. The collected data related to age, duration of hemodialysis, duration of administration of erythropoietin, dose of erythropoietin, response to the dose of erythropoietin, values of erythrocytes, hematocrit and albumin. The study

Tabela 1. Demografske, kliničke i terapijske karakteristike ispitanika na hemodijalizi koji primaju tromesečnu terapiju eritropoetina u cilju lečenja anemije

Varijabla	Grupa 1 (n=21) AS ± SD	Grupa 2 (n=31) AS ± SD	t-test	p vrednost
Starost (godine)	56,71 ± 13,24	57,32 ± 11,97	-0,172	0,864
Dužina trajanja hemodijalize (godine)	6,10 ± 5,47	5,24 ± 4,71	0,604	0,549
Dužina trajanja terapije EPO (godine)	5,67 ± 5,58	5,07 ± 4,52	0,427	0,549
Doza EPO (IJ/kg telesne mase)	121,65 ± 63,17	176,44 ± 92,78	-2,358	0,022
Odgovor na terapiju EPO (IJ/kg telesne mase)	1,28 ± 0,87	0,95 ± 1,31	1,000	0,322
ITM (kg/m^2)	21,93 ± 3,10	24,18 ± 5,26	-1,924	0,050
Debljina kožnog nabora (mm)	18,44 ± 21,72	19,82 ± 11,04	-0,300	0,766
Obim nadlaktice (mm)	25,39 ± 3,74	26,44 ± 3,54	-0,987	0,329
Transferin (mg/dl)	0,61 ± 0,34	0,81 ± 0,74	-1,114	0,271
Broj eritrocita (x 10^{12})	3,43 ± 0,39	3,29 ± 0,57	0,768	0,438
Albumini (g/dl)	36,48 ± 3,73	36,28 ± 2,35	0,168	0,868
Hemoglobin (g/l)	95,02 ± 8,41	91,58 ± 15,23	0,804	0,428
Hematokrit (l/l)	0,29 ± 0,028	0,28 ± 0,05	0,854	0,400
Gvožđe (mmol/l)	8,68 ± 3,99	7,68 ± 3,27	0,735	0,468

AR- aritmetička sredina; SD- standardna devijacija; grupa 1 (osobe na hemodijalizi sa vrednostima hemoglobina ≥ 110 g/l i više); grupa 2 (osobe na hemodijalizi sa vrednostima hemoglobina nižim od 110 g/l); EPO – eritropoetin; ITM – indeks telesne mase.

je postignuta ciljana vrednost hemoglobina od 110 g/l ili više (grupa 1), a kod 59,6% ciljne vrednosti hemoglobina nisu postignute (grupa 2). Ispitanici grupe 2 su primali značajno veće prosečne doze eritropoetina i imali nešto veći indeks telesne mase (ITM) nego ispitanici grupe 2. Između ispitivanih grupa nije bilo značajne razlike u odnosu na odgovor na eritropoetin, dužinu trajanja terapije eritropoetinom, dužinu trajanja hemodijalize, starost ispitanika, debljinu kožnog nabora, obim nadlaktice, vrednosti transferina, broj eritrocita, vrednosti albumina, hemoglobina, hamatokrita i gvožđa.

Diskusija

Cilj ovog istraživanja je bio da se ispitaju faktori koji utiču na oporavak od anemije osoba na hemodijalizi, a koje su na terapiji rekombinantnim eritropoetinom, kako bi se eventualnim uklanjanjem ovih faktora olakšao oporavak od anemije. Prema rezultatima našeg istraživanja postoji značajna razlika u prosečnoj dozi rekombinantnog eritropoetina između osoba na hemodijalizi kod kojih je postignuta ciljna vrednost hemoglobuna (grupa 1) i onih kod kojih nije (grupa 2). Prosečna doza primanog eritropoetina za prvu grupu ispitanika (121,65 ± 63,17 IJ/kg) je bila u okviru preporučenih i za supkutanu i za intravensku primenu,

Table 1. Demographic, clinical and treatment characteristics of participants on hemodialysis who receive a three-month erythropoietin treatment aimed at treating anemia

Variable	Group 1 (n=21) AS ± SD	Group 2 (n=31) AS ± SD	t-test	p vrednost
Age (years)	56.71 ± 13.24	57.32 ± 11.97	-0.172	0.864
Duration of hemodialysis (years)	6.10 ± 5.47	5.24 ± 4.71	0.604	0.549
Duration of EPO therapy (years)	5.67 ± 5.58	5.07 ± 4.52	0.427	0.549
Dose of EPO (IU/kg body weight)	121.65 ± 63.17	176.44 ± 92.78	-2.358	0.022
Response to EPO therapy (IU/kg body weight)	1.28 ± 0.87	0.95 ± 1.31	1.000	0.322
BMI (kg/m^2)	21.93 ± 3.10	24.18 ± 5.26	-1.924	0.050
Skin-fold thickness (mm)	18.44 ± 21.72	19.82 ± 11.04	-0.300	0.766
Upper arm width (mm)	25.39 ± 3.74	26.44 ± 3.54	-0.987	0.329
Transferrin (mg/dl)	0.61 ± 0.34	0.81 ± 0.74	-1.114	0.271
Number of erythrocytes (x 10^{12})	3.43 ± 0.39	3.29 ± 0.57	0.768	0.438
Albumin (g/dl)	36.48 ± 3.73	36.28 ± 2.35	0.168	0.868
Hemoglobin (g/l)	95.02 ± 8.41	91.58 ± 15.23	0.804	0.428
Hematocrit (l/l)	0.29 ± 0.028	0.28 ± 0.05	0.854	0.400
Iron (mmol/l)	8.68 ± 3.99	7.68 ± 3.27	0.735	0.468

AM- arithmetic mean; SD- standard deviation; group 1 (persons on hemodialysis with haemoglobin values ≥ 110 g/l and higher); group 2 (persons on hemodialysis with haemoglobin values lower than 110 g/l); EPO – erythropoietin; BMI – body mass index.

was approved by the Ethical Committee of the Clinical Center of Montenegro. Student's t-test was used in the statistical analysis of data.

Results

The cross-sectional study included 52 persons on hemodialysis who were treated due to anemia with the administration of erythropoietin (Table 1). After the administered erythropoietin, the target hemoglobin value of 110 g/l or higher was achieved only in 21 patients (40.4%) (group 1), while in 59.6% of patients the target hemoglobin values were not achieved (group 2). The participants from group 2 received significantly higher average doses of erythropoietin and had a little bit higher body mass index (BMI) than participants in group 2. There was no significant difference between the examined groups regarding their response to erythropoietin, duration of treatment with erythropoietin, duration of hemodialysis, participants' age, thickness of skin folds, upper arm width, transferrin values, number of erythrocytes, value of albumin, hemoglobin, hematocrit and iron.

Discussion

The aim of this study was to investigate factors that affect the recovery from anemia in persons undergoing hemodialysis, and who received

dok su za drugu grupu (176,44 ± 92,78 IJ/kg) bile u okviru dozvoljenih za intravensku primenu. Vrednosti eritropoetina za drugu grupu ispitanika su iznad preporučene doze i za supkutanu i za intravensku primenu, što može da ukaže da kod ovih ispitanika postoji rezistencija anemije na lek. Ukoliko su potrebne doze eritropoetina veće od 150 IJ/kg, tri puta nedjeljno, smatra se da postoji rezistencija prema eritropoetinu (14,22). Anemija rezistentna na preporučene doze eritropoetina (22), uz dovoljnu količinu gvožđa i vitamina, često ukazuje na neadekvatnu dijalizu, nekontrolisani hiperparatireoidizam, trovanje aluminijumom, hronični gubitak krvi ili hemolizu i propratnu hemoglobinopatiju, malnutriciju, hroničnu infekciju, multipli mijelom ili druge malignitete. Terapija eritropoetinom se vrlo dobro podnosi, kako subjektivno, tako i objektivno, i ima mnogo prednosti u odnosu na transfuzije krvi, čija primena može biti praćena brojnim neželjenim posledicama. Transfuzije krvi mogu doprineti supresiji eritropoeze u HBI, zato što povećavaju rizik od hepatitisa, hemosideroze i odbacivanja transplantata, pa ih treba izbegavati dok bolesnik ne odgovori na terapiju eritropoetinom i osoba ne ispolji simptomatologiju (22). Korekcija anemije dovodi do poboljšanja kardijalne hemodinamike, poboljšanja fizičke kondicije i radnog kapaciteta. Iako postoje razlike u prosečnoj dozi eritropoetina između ispitivanih grupa, to nije uticalo da se dobiju značajne razlike između grupa u odnosu na vrednosti eritrocita, hemoglobina i hematokrita.

U našem istraživanju, nije bilo značajne razlike u odnosu na uzrast između osoba na hemodijalizi sa postignutim ciljnim vrednostima hemoglobina (56,71 ± 13,24 godina) i onih kod kojih ciljna vrednost nije ostvarena (57,32 ± 11,97 godina). Rezultati brojnih studija pokazuju da su osobe koje se leče dijalizom i kod nas i u svetu sve starije osobe (23-25).

Uočava se da su osobe na hemodijalizi koje su postigle adekvatan odgovor na terapiju eritropoetinom (grupa 1) imale značajno niži indeks telesne mase nego osobe bez adekvatnog odgovora na terapiju eritropoetinom (grupa 2), iako su obe grupe ispitanika pripadale grupi normalno uhranjenih osoba (vrednosti indeksa telesne mase za normalno uhranjene se kreću od 18,5 do 24,9 kg/m^2). U studiji *El-Kannishy* i saradnika, multicentrična studija koja je objedinila podatke 9 centara za hemodijalizu u Egiptu, pokazala je, takođe, da su gojazne osobe (indeks telesne mase ≥ 30 kg/m^2) koje su na hemodijalizi ređe (25,3 %) primenom eritropoetina ostvarivale ciljne vrednosti hemoglobina (10,0–11,5 g/dL) nego negojazne osobe (27,3 %), ali uočena razlika nije bila statistički značajna (26). Između ovih grupa nije bilo značajne razlike u prosečnim vrednostima serumskog feritina i indeksu zasićenosti transferinom, ali je nedeljna doza eritropoetina bila značajno niža kod gojaznih nego negojaznih osoba. U većini do sada sprovedenih istraživanja ukazuje se da je stopa incidencije i prevalencija gojaznih mnogo veća među osobama na hemodijalizi (preko 30%), nego u opštoj populaciji (7,28), što zahteva istraživanja o vezi između gojaznosti, anemije i odgovora na eritropoetin kod osoba na hemodijalizi. U zemljama u razvoju, anemija kod osoba na hemodijalizi može biti pogoršana ishranom, kao i većom učestalošću zaraznih bolesti.

Nedostaci ovog istraživanja odnose se na sprovođenje same studije preseka (u ovim studijama nismo sigurni šta je uzrok, a šta posledica) i nemoćunosti dobijanja podataka za veći broj varijabli koje mogu da se dovedu u vezu sa adekvatnim odgovorom anemije na terapiju eritropoetinom. Takođe, ovo istraživanje je sprovedeno na malom broju ispitanika. Zahvaljujući ovom istraživanju, otvorene su mogućnosti za dalja istraživanja u ovoj oblasti. Rezultati istraživanja pokazuju da rezistencija na terapiju eritropoetinom i veći indeks telesne mase mogu biti razlog za neadekvatan odgovor anemije kod osoba na hemodijalizi.

Zaključak

Neophodna su dalja istraživanja u ovoj oblasti, posebno kliničke studije, koje bi ukazale na sve faktore koji onemogućuvaju adekvatan odgovor anemije na terapiju hematopoetinom.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

Literatura

1. Jacović S, Jovanović M, Hamzagić N, Pavlović R, Petrović D. Rezistencija na eritropoetin kod bolesnika na hemodijalizi. Acta Facultatis Medicae Naissensis 2019; 36(1):5-14. doi: 10.2478/afmnai-2019-0001
2. Sosnin DY, Khovaeva YB, Podyanova AI, Syromyatnikova TN, Nenasheva OY. [Eritropoetin as laboratory index of the degree of respiratory insufficiency in chronic obstructive pulmonary diseases.]. Klin Lab Diagn 2018; 63(11):691-5. doi: 10.18821/0869-2084-2018-63-11-691-695.

recombinant erythropoietin, so that the recovery from anemia might be improved with the possible elimination of these factors. According to the results of our research, there is a significant difference in the average dose of recombinant erythropoietin between persons on hemodialysis, in whom the target hemoglobin value was achieved (group 1), and those patients, in whom the target value was not achieved (group 2). The average dose of administered erythropoietin for the first group of participants (121.65 ± 63.17 IU/kg) was within the recommended range for both the subcutaneous and intravenous application, while in the second group of participants (176.44 ± 92.78 IU/kg), it was within the range allowed for the intravenous application. The values of erythropoietin for the second group of participants were above the recommended dose for both the subcutaneous and intravenous application, which may indicate that there is resistance of anemia to this medication in these patients. If the necessary doses of erythropoietin are higher than 150 IU/kg three times a week, it is deemed to be the resistance to erythropoietin (14,22). Anemia which is resistant to the recommended doses of erythropoietin (22), with the sufficient amount of iron and vitamins, often points to the inadequate dialysis, uncontrolled hyperthyroidism, poisoning with aluminum, chronic blood loss or hemolysis and accompanying hemoglobinopathy, malnutrition, chronic infection, multiple myeloma, or other malignancies. The therapy of erythropoietin is often well-tolerated, subjectively and objectively, and it has numerous advantages in comparison to blood transfusion, whose application may be accompanied by numerous side effects. Blood transfusion may contribute to the suppression of erythropoiesis in chronic kidney disease, because it increases the risk of hepatitis, hemosiderosis, and transplant rejection, and therefore, it should be avoided until anemia responds to the therapy with erythropoietin and the symptoms appear (22). The correction of anemia leads to the improvement of cardiovascular hemodynamics, physical strength and work capacity. Although there are differences in the average dose of erythropoietin between the examined groups, it did not influence obtaining significant difference between the groups regarding the values of erythrocytes, hemoglobin and hematocrit.

In our study, there was no significant difference regarding the age between persons on hemodialysis with the achieved target values of hemoglobin (56.71 ± 13.24 years) and those in whom the target value was not achieved (57.32 ± 11.97). The results of numerous studies have shown that persons undergoing dialysis belong to the group of elderly in the world and in our country, as well (23-25).

It has been noticed that persons on hemodialysis, who achieved an adequate response to treatment with erythropoietin (group 1) had a significantly lower body mass index than persons who did not respond adequately to erythropoietin (group 2), although both groups of participants belonged to the group of persons with normal body weight (values of body mass index for normal weight range from 18.5 to 24.9 kg/m^2). In the study of El-Kannishy and associates, which is a multicentric study which coalesced data from 9 centers for hemodialysis in Egypt, showed that overweight persons (body mass index > 30 kg/m^2) on hemodialysis achieved more rarely (25.3%) the target values of hemoglobin (10.0 - 11.5 g/dL) than persons who were not overweight (27.3%), but the difference was not statistically significant (26). There was no significant difference between these groups regarding the values of serum ferritin, and transferrin saturation index, but the weekly dose of erythropoietin was significantly lower in overweight persons than in persons who were not overweight. In most of the research studies, which have been conducted so far, the incidence and prevalence rate was higher in persons on hemodialysis (more than 30%) than in the general population (7,28), which requires further research about the relationship between obesity, anemia and response to erythropoietin in persons on hemodialysis. In developing countries, anemia in persons on hemodialysis may be worsened because of the diet and higher frequency of infectious diseases.

The limitations of this research relate to the characteristics of cross-sectional studies (in these studies we are not certain about causes and consequences) and the impossibility of obtaining data for more variables that may be linked to the adequate response of anemia to erythropoietin therapy. Also, this study included a small number of participants. Thanks to this research, new possibilities have been opened for further research in this field. The results of research showed that the resistance to erythropoietin and higher body

3. Sakaguchi Y, Hamano T, Wada A, Masakane I. Types of Erythropoietin-Stimulating Agents and Mortality among Patients Undergoing Hemodialysis. J Am Soc Nephrol 2019; 30(6):1037-48. doi: 10.1681/ASN.2018101007
4. Georgianos PI, Agarwal R. Systolic and diastolic hypertension among patients on hemodialysis: Musings on volume overload, arterial stiffness, and erythropoietin. Semin Dial 2019; 32(6):507-12. doi: 10.1111/sdi.12837
5. Aapro M, Krendyukov A, Schiestl M, Gascón P. Epoetin Biosimilars in the Treatment of Chemotherapy-Induced Anemia: 10 Years' Experience Gained. BioDrugs 2018; 32(2):129-35. doi: 10.1007/s40259-018-0262-9
6. Nafar M, Samavat S, Khoshdel A, Alipour-Abedi B. Anemia Evaluation and Erythropoietin Dose Requirement Among Hemodialysis Patients: a Multicenter Study. Iran J Kidney Dis 2017;11(1):56-65. PMID: 28174354.
7. Mimran A. Renal effects of antihypertensive agents in parenchimal renal disease and renovascular hypertension. J Cardiovasc Pharmacol 1992; 19(suppl 6): 45-50. doi: 10.1097/00005344-199219006-00009.
8. Veys N, Dhondt A, Lameire N. Pain at the injection site of subcutaneously administered erythropoietin: phosphate-buffered epoetin alpha compared to citrate-buffered epoetin alpha and epoetin beta. Clin Nephrol 1998; 49(1):41-4.
9. Weiss LG, Clyne N, Divino Fihlho J, Frisenette-Fich C, Kurkus J, Svensson B. 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 2000; 15(12):2014-9. doi: 10.1093/ndt/15.12.2014.
10. Locatelli F, Andrulli S, Memoli B, Maffei C, Del Vecchio L, Aterini S, et al. Nutritional-inflammation status and resistance to erythropoietin therapy in haemodialysis patients. Nephrol Dial Transplant 2006; 21(4):991-8. doi: 10.1093/ndt/gfk011
11. Besarab A, Reyes CM, Hornberger J. Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in hemodialysis patients. Am J Kidney Dis 2002; 40(3):439-46. doi: 10.1053/ajkd.2002.34881
12. Goldsmith D and O' Donoghue D. Optimizing hemoglobin control with erythropoesis-stimulating agent: results of the Subcutaneus Erythropoetin Control (SEC) study. Presented at ASN Philadelphia, USA; 2005.
13. Ebben JP, Gilbertson DT, Foley RN, Collins AJ. Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. Clin J Am Soc Nephrol 2006; 1(6):1205-10. doi: 10.2215/CJN.01110306
14. KDOQI. Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. Am J Kidney Dis 2006; 47(5 Suppl 3):16-85. doi: 10.1053/j.ajkd.2006.03.011.
15. Petković N, Ristić S, Stošović M, Đukanović L. Razlike u odgovoru bolesnika lečenih hemodijalizama na humani rekombinovani eritropoetin. Medicinski pregled 2013; 66(3-4):130-7. doi: 10.2298/MPNS1304130P
16. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006; 355(20):2071-84. doi: 10.1056/NEJMoa062276
17. Ifudu O, Feldmann J, Friedman EA. The intensity of haemodialysis and the response to erythropoietin in patients with end-stage renal disease. N Engl J Med 1996; 334:420-5. doi: 10.1056/NEJM199602153340702
18. Sowade B, Sowade O, Mocks J, Franke W, Warnke H. The safety of treatment with recombinant human erythropoeitin in clinical use: a review-controlled studies. Int J Med 1998; 1: 303-14. doi: 10.3892/ijmm.1.2.303.
19. Choukroun G. Pain at the injection site: Results of the first cross-over study comparing epoetin beta and darbepoetin alfa administered subcutaneously in healthy volunteers. Presented at XLII ERA-ADTA congress, Istambul, Turkey; 2005.
20. Schmitt CP, Nau B, Brummer C, Rosenkranz J, Schaefer F. Increased injection pain with darbepoetin-alpha compared to epoetin-beta in paediatric dialysis patients. Nephrol Dial Transplant 2006; 21(12):3520-4. doi: 10.1093/ndt/gfl479
21. Stosevic M. Uporedna analiza indeksa adekvatnosti dijalize upotrebom kliničkih parametara pri raznim nivoima dijaliziranosti kod bolesnika na hemodijalizi. Doktorska disertacija, Medicinski fakultet Univerziteta u Beogradu; 2002.
22. Djukanovic L, Lezaic V. Liječenje anemije kod bolesnika sa hroničnom insuficijencijom bubrega rekombinantnim eritropoetinom. Srp arh 1996; 124:93-7.
23. Ratković M. Procjena kvaliteta liječenja bolesnika sa terminalnom bubrežnom insuficijencijom hemodijalizama. Doktorska disertacija, Medicinski fakultet Univerziteta u Beogradu; 2002.
24. Valderrabano F. Quality of life benefits of early anaemia treatment. Nephrol Dial Transplant 2000; 15(Supll 3):23-8. doi: 10.1093/oxfordjournals.ndt.a027972
25. Priyadarshi A, Shapiro JI. Erythropoietin resistance in the treatment of the anemia of chronic renal failure. Semin Dial 2006; 19(4):273-8. doi: 10.1111/j.1525-139X.2006.00172.x
26. El-Kannishy GM, Megahed AF, Tawfik MM, El-Said G, Zakaria RT, Mohamed NA, et al. Obesity may be erythropoietin dose-saving in hemodialysis patients. Kidney Res Clin Pract 2018; 37(2):148-56. doi: 10.23876/j.krcp.2018.37.2.148.
27. Kramer HJ, Saranathan A, Luke A, Durazo-Arvizu RA, Guichan C, Hou S, Cooper R. In-creasing body mass index and obesity in the incident ESRD population. J Am Soc Neph-rol 2006; 17:1453–9. doi: 10.1681/ASN.2005111241.
28. Lorenzo V, Martin M, Rufino M, Sanchez E, Jiménez A, Hernández D, Torres A. High prevalence of overweight in a stable Spanish hemodialysis population: a cross sectional study. J Ren Nutr 2003; 13:52–9. doi: 10.1053/jren.2003.50004.

mass index may be the reason for the inadequate response of anemia in persons on hemodialysis.

Conclusion

Further research in this field is necessary, especially clinical trials, which would point to all factors that make it impossible to adequately respond to the therapy of hematopoietin in anemia.

Competing interests

Authors declare no competing interests.

Literature

1. Jacović S, Jovanović M, Hamzagić N, Pavlović R, Petrović D. Rezistencija na eritropoetin kod bolesnika na hemodijalizi. Acta Facultatis Medicae Naissensis 2019; 36(1):5-14. doi: 10.2478/afmnai-2019-0001
2. Sosnin DY, Khovaeva YB, Podyanova AI, Syromyatnikova TN, Nenasheva OY. [Eritropoetin as laboratory index of the degree of respiratory insufficiency in chronic obstructive pulmonary diseases.]. Klin Lab Diagn 2018; 63(11):691-5. doi: 10.18821/0869-2084-2018-63-11-691-695.
3. Sakaguchi Y, Hamano T, Wada A, Masakane I. Types of Erythropoietin-Stimulating Agents and Mortality among Patients Undergoing Hemodialysis. J Am Soc Nephrol 2019; 30(6):1037-48. doi: 10.1681/ASN.2018101007
4. Georgianos PI, Agarwal R. Systolic and diastolic hypertension among patients on hemodialysis: Musings on volume overload, arterial stiffness, and erythropoietin. Semin Dial 2019; 32(6):507-12. doi: 10.1111/sdi.12837
5. Aapro M, Krendyukov A, Schiestl M, Gascón P. Epoetin Biosimilars in the Treatment of Chemotherapy-Induced Anemia: 10 Years' Experience Gained. BioDrugs 2018; 32(2):129-35. doi: 10.1007/s40259-018-0262-9
6. Nafar M, Samavat S, Khoshdel A, Alipour-Abedi B. Anemia Evaluation and Erythropoietin Dose Requirement Among Hemodialysis Patients: a Multicenter Study. Iran J Kidney Dis 2017;11(1):56-65. PMID: 28174354.
7. Mimran A. Renal effects of antihypertensive agents in parenchimal renal disease and renovascular hypertension. J Cardiovasc Pharmacol 1992; 19(suppl 6): 45-50. doi: 10.1097/00005344-199219006-00009.
8. Veys N, Dhondt A, Lameire N. Pain at the injection site of subcutaneously administered erythropoietin: phosphate-buffered epoetin alpha compared to citrate-buffered epoetin alpha and epoetin beta. Clin Nephrol 1998; 49(1):41-4.
9. Weiss LG, Clyne N, Divino Fihlho J, Frisenette-Fich C, Kurkus J, Svensson B. 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 2000; 15(12):2014-9. doi: 10.1093/ndt/15.12.2014.
10. Locatelli F, Andrulli S, Memoli B, Maffei C, Del Vecchio L, Aterini S, et al. Nutritional-inflammation status and resistance to erythropoietin therapy in haemodialysis patients. Nephrol Dial Transplant 2006; 21(4):991-8. doi: 10.1093/ndt/gfk011
11. Besarab A, Reyes CM, Hornberger J. Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in hemodialysis patients. Am J Kidney Dis 2002; 40(3):439-46. doi: 10.1053/ajkd.2002.34881
12. Goldsmith D and O' Donoghue D. Optimizing hemoglobin control with erythropoesis-stimulating agent: results of the Subcutaneus Erythropoetin Control (SEC) study. Presented at ASN Philadelphia, USA; 2005.
13. Ebben JP, Gilbertson DT, Foley RN, Collins AJ. Hemoglobin level variability: associations with comorbidity, intercurrent events, and hospitalizations. Clin J Am Soc Nephrol 2006; 1(6):1205-10. doi: 10.2215/CJN.01110306
14. KDOQI. Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. Am J Kidney Dis 2006; 47(5 Suppl 3):16-85. doi: 10.1053/j.ajkd.2006.03.011.
15. Petković N, Ristić S, Stošović M, Đukanović L. Razlike u odgovoru bolesnika lečenih hemodijalizama na humani rekombinovani eritropoetin. Medicinski pregled 2013; 66(3-4):130-7. doi: 10.2298/MPNS1304130P
16. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006; 355(20):2071-84. doi: 10.1056/NEJMoa062276
17. Ifudu O, Feldmann J, Friedman EA. The intensity of haemodialysis and the response to erythropoietin in patients with end-stage renal disease. N Engl J Med 1996; 334:420-5. doi: 10.1056/NEJM199602153340702
18. Sowade B, Sowade O, Mocks J, Franke W, Warnke H. The safety of treatment with recombinant human erythropoeitin in clinical use: a review-controlled studies. Int J Med 1998; 1: 303-14. doi: 10.3892/ijmm.1.2.303.
19. Choukroun G. Pain at the injection site: Results of the first cross-over study comparing epoetin beta and darbepoetin alfa administered subcutaneously in healthy volunteers. Presented at XLII ERA-ADTA congress, Istambul, Turkey; 2005.
20. Schmitt CP, Nau B, Brummer C, Rosenkranz J, Schaefer F. Increased injection pain with darbepoetin-alpha compared to epoetin-beta in paediatric dialysis patients. Nephrol Dial Transplant 2006; 21(12):3520-4. doi: 10.1093/ndt/gfl479
21. Stosevic M. Uporedna analiza indeksa adekvatnosti dijalize upotrebom kliničkih parametara pri raznim nivoima dijaliziranosti kod bolesnika na hemodijalizi. Doktorska disertacija, Medicinski fakultet Univerziteta u Beogradu; 2002.
22. Djukanovic L, Lezaic V. Liječenje anemije kod bolesnika sa hroničnom insuficijencijom bubrega rekombinantnim eritropoetinom. Srp arh 1996; 124:93-7.

Primljen: 15.09.2022. **Revizija:** 19.09.2022. **Prihvaćen:** 20.09.2022.

23. Ratković M. Procjena kvaliteta liječenja bolesnika sa terminalnom bubrežnom insuficijencijom hemodijalizama. Doktorska disertacija, Medicinski fakultet Univerziteta u Beogradu; 2002.
24. Valderrabano F. Quality of life benefits of early anaemia treatment. Nephrol Dial Transplant 2000; 15(Supll 3):23-8. doi: 10.1093/oxfordjournals.ndt.a027972
25. Priyadarshi A, Shapiro JI. Erythropoietin resistance in the treatment of the anemia of chronic renal failure. Semin Dial 2006; 19(4):273-8. doi: 10.1111/j.1525-139X.2006.00172.x
26. El-Kannishy GM, Megahed AF, Tawfik MM, El-Said G, Zakaria RT, Mohamed NA, et al. Obesity may be erythropoietin dose-saving in hemodialysis patients. Kidney Res Clin Pract 2018; 37(2):148-56. doi: 10.23876/j.krcp.2018.37.2.148.
27. Kramer HJ, Saranathan A, Luke A, Durazo-Arvizu RA, Guichan C, Hou S, Cooper R. In-creasing body mass index and obesity in the incident ESRD population. J Am Soc Neph-rol 2006; 17:1453–9. doi: 10.1681/ASN.2005111241.
28. Lorenzo V, Martin M, Rufino M, Sanchez E, Jiménez A, Hernández D, Torres A. High prevalence of overweight in a stable Spanish hemodialysis population: a cross sectional study. J Ren Nutr 2003; 13:52–9. doi: 10.1053/jren.2003.50004.

Received: 09/15/2022 **Revised:** 09/19/2022 **Accepted:** 09/20/2022