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Effects of rHuEPO Treatment on Red Blood Cell Osmotic Resistance

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A B S T R A C T

Red blood cell osmotic resistance (RBCOR) is defined as resistance to osmotic changes in cell integrity after their exposure to hypotonic saline solution. The investigation examined the effect of rHuEPO on RBCOR in hemodialysed patients. The study included 58 patients aged 49±14 years, treated by hemodialysis for 59±43 months on average. Half of the patients received rHuEPO for anemia correction. RBCOR was determined in all patients as 3 values: hemolysis start point (HSP), hemolysis end point (HEP) and middle osmotic resistance (MOR). The patients underwent laboratory checkup for parameters characteristically changed in the uremic syndrome. In the control group of healthy subjects (n=16) RBCOR was only determined. No differences were found in the average values of HSP, HEP and MOR between the rHuEPO treated group of patinets and the untreated group. Compared to healthy individuals, the hemodialysed patients displayed significantly higher values of HSP, HEP and MOR. The only one significant correlation of RBCOR and routine laboratory features was found between MOR and predialytic serum concentrations of calcium ($r=0.28$, $p<0.05$) and hydrogen ions ($r=0.37$, $p<0.05$). Our results suggest that the administration of rHuEPO does not affect RBCOR in hemodialysed patients, that RBCOR is not always reduced in this population and that it correlates with a small number of laboratory parameters characteristic for the uremic syndrome.

***Key words**: red blood cell osmotic resistance, rHuEPO, ESRD, hemodialysis*

Introduction

Red blood cell osmotic resistance (RBCOR) is an *in vitro* property of erythrocytes to retain their integrity by resisting the osmotic pressure that drives wa-

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ter into the cell when exposed to hypotonic saline solutions. The *in vivo* role of hypotonic saline solutions is taken over by plasma, although it is not hypotonic. Both *in vivo* and *in vitro*, this property depends on the medium surrounding the RBC, as well as on the cell membrane features. End-stage renal disease (ESRD) patients tend to have reduced RBCOR, but it is not a rule[1–9]. Together with a reduced ability of RBC to change their form while passing through nutritive capillaries[10] whose diameters are lower than those of the RBC[11], i.e. with diminished deformability, it reduces RBC life span and leads to anemia.

On average, the life span of RBC in ESRD patients is only half of that in healthy individuals[12]. This characteristic, however, may be a contributing, but not the sole factor responsible for anemia, a common finding in patients with chronic renal failure (CRF)[13]. Anemia usually becomes manifest at creatinine clearance level below 40 ml/min/ 1.73 m^2 of body surface and is aggravated with further deterioration of renal function[14]. Although the level of anemia may vary considerably in patients at the same stage of renal failure, it is believed that primary renal disease, with the exception of autosomal dominant polycystic kidney disease (ADPKD), does not determine the occurrence of anemia[15]. The cause of anemia is ascribed to several mechanisms. Those mechanisms either inhibit RBC production (decreased erythropoietin production[16], iron, folic acid, vitamin B_{12} and L-carnitine deficiency[4,17], secondary hyperparathyroidism[18–19], circulating uremic erythropoiesis inhibitors[20–25] and aluminum toxicity[26]), or, as it is already mentioned, shorten the RBC life span (hemolysis[3,27], hypersplenism[28]). By far the most important factor is the erythropoietin shortage[4,16,29–33].

The commonly used term for RBCOR is RBC osmotic fragility (RBCOF). High osmotic resistance denotes low osmotic fragility and vice versa.

Forty years ago it was believed that RBCOR was only affected by uremic plasma, because it was found that the RBC of uremic individuals had normal life span after being transfused into healthy persons, whereas the RBC of normal individuals had shortened life span after being transfused into uremic patients[34–36]. It was thought that uremic plasma inhibited the activity of Na-K pump of RBC[37], which, together with membrane lipids, retained their biconcave shape and protected them from hemolysis[3]. Cheng et al[38] found that the number of these pumps was lower at the RBC surface in uremic patients compared to healthy persons. Dialysis regulates RBCOR by removing uremic toxins of low molecular mass, reducing serum parathyroid hormone concentration, reducing calcium influx into RBC[39], decreasing plasma osmolality[2] and increasing RBC fluidity[10,40]. Recent studies have demonstrated that RBCOR in CRF may also be affected through the RBC membrane metabolism by administering antioxidant substances like vitamin E[41–42], vitamin C and zinc[43], and correcting serum L-carnitine level[1,4–6]. The results of the studies that investigate the effects of rHuEPO on RBCOR in CRF are not concordant: they either show no influence of rHuEPO on RBCOR in this population[5] or they demonstrate an improvement of RBCOR[44–45] under rHuEPO.

This paper attempts to evaluate the effect of rHuEPO on RBCOR, the frequency of reduced RBCOR in the population of ESRD patients treated with HD, and the correlation with laboratory parameters characteristic for an abnormal in uremic syndrome.

Patients and Methods

The study included 58 ESRD patients (29 women and 29 men), aged between 20

to 70 years (49±14 years in average), treated with bicarbonate HD for 59±43 months on average (range 9–176 months), three times a week for 4–4.5 hours using dialyzers made of modified cellulose acetate or diacetate (n=51), or of polysulphone (n=7), with surface area of 1.3–1.7 m^2, with blood flow of 250–300 ml/min and dialysate flow of 500 ml/min. All dialyzers were sterilized with ethyl oxide. The water for dialysis was prepared with reversed osmosis. Conductivity below 10 µS/cm was ensured. The microbiological quality of water for dialysis and of dialysate was determined twice monthly.

Half of the patients received rHuEPO for anemia correction for more than six months. Twelve of the 29 patients that received rHuEPO and 11 of the 29 patients without rHuEPO, were treated with calcium channel blockers. Patients with autoimmune diseases, patients with hemolytic anemia and patients transfused in the last 3 months were excluded. The control group consisted of 16 employers of the dialytic center.

CRF was the consequence of chronic glomerulonephritis in 31 patients (53.45%), diabetes mellitus in 8 (13.79%), chronic interstitial nephritis in 9 (15.52%), arterial hyper-tension in 4 (6.89%), ADPKD in 3 (5.17%), and of other kidney diseases in 3 patients (5.17%).

RBCOR was measured using a spectrophotometric technique (Dacie and Lewis[46]), whereas the RBC count, hemoglobin concentration, hematocrit, reticulocyte proportion, mean corpuscular volume (MCV) were determined for each patient with the automatic cell counter (Coulter Counter). Each patient also underwent determination of serum iron con-centration (women 8–30 µmol/l, men 11–32 µmol/l), using a photocolorimetric method with 2,4,6-three(2-pyridyl)-5-threeazine, TIBC (50–72 µmol) using a magnesium-hydro-xicarbonate method, serum urea concentration (3.40–8.00 mmol/l) using an enzymatic UV method with urease and glutamate dehydrogenase, creatinine (42–115 µmol/l) using an enzymatic colorimetric PAP procedure, potassium (3,6–5,6 mmol/l) using a flaming spectrophotometry, calcium (2.25–2.75 mmol/l) using colorimetry with ortocresolphtalein, phosphates (0.80–1.40 mmol/l) using a molibdate UV method, alkaline phosphatase (women 40–110 U/L, men 43–88 U/l) using IFCC recommended method with AMP buffer, arterial acidbase state, bilirubin (4–20 µmol/l) by DPD method with 2.5 diclorphenildiazonim, i-PTH (8–76 pg/ml) (ELSA PTH, immunoradiometric assay, GIF-SUR-YVETTE CEDEX, France) and plasma osmolality {(plasma osmolality (mmol/l) = 2 × (serum sodium concentration + serum potassium concentration) + serum urea concentration + serum glucose concentration} (mmol/l)[47]. Control subjects underwent RBCOR determination only.

For each patient and control subject saline solution concentrations were determined from the RBCOR test at three 3 values: hemolysis start point (HSP) – saline solution concentration at the moment of starting hemolysis, hemolysis end point (HEP) – saline solution concentration at the moment of terminating hemolysis, and middle osmotic resistance (MOR) – saline solution concentration needed for the lysis of 50% of RBC) (normal values are in the Table 1). Lower RBCOR is characterized by higher HSP, HEP and MOR values.

The obtained results expressed as arithmetic mean values, standard deviations and as frequencies were analyzed using a t-test and a Chi-square test, whereas individual values were analyzed with a correlation test. Statistical significance was assessed at the level of 1 and 5% ($p<0.01$, $p<0.05$)[48].

Results

In the group of 58 hemodialysed patients 50% of RBC lysed (MOR) at saline concentration of 0.44±0.07%. HSP was recorded at saline concentration of 0.52± 0.09%, and HEP at 0.31±0.05%. Mean MOR, HSP and HEP values in the hemodialysed patients were significantly higher than in the healthy control individuals (MOR: 0.44±0.07% : 0.37±0.02%; t= 6.69, p<0.01; HSP: 0.52±0.09% : 0.44± 0.02%; t=6.23, p<0.01; HEP: 0.31±0.05% : 0.28±0.02%; t=3.64, p<0.01) (Table 2). Moreover, 22 of the 58 patients (37.93%) had normal MOR values, 17 had normal HSP values (29.31%) and 19 normal HEP values (32.76%). Correlation tests revealed only a statistically significant positive correlation between MOR and predialysis serum calcium concentrations (r=0.275, p<0.05) and hydrogen serum concentrations (r=0.372, p<0.01).

TABLE 1
NORMAL VALUES OF RED BLOOD CELL OSMOTIC RESISTANCE (RBCOR)

Parameter	Normal values (% of saline solution)
Hemolysis start point – HSP	0.50–0.44%
Hemolysis end point – HEP	0.34–0.30%
Middle osmotic resistance – MOR	0.33–0.41%

There was no difference in the mean MOR, HSP and HEP values in the patients receiving rHuEPO and in the patients without the rHuEPO treatment (Table 3). According to the Chi-square test, among the rHuEPO treated patients the number of those with normal values of MOR (12/29:10/29), HSP (9/29:8/29) and HEP (9/29:10/29) was not statistically higher compared to non-rHuEPO treated patients (Table 4). Statistically, the rHuEPO treated patients were significantly younger in comparison with patients without rHuEPO treatment, had higher hematocrit values, more severe acidosis and higher urea and potassium predialysis serum concentrations. (Table 3).

At almost identical saline concentrations were needed for hemolysis of 50% of RBC in HD patients (0.44±0.07%) and for starting hemolysis in healthy control subjects (0.44±0.02%). Moreover, the range from initial to complete hemolysis in HD patients was significantly higher (0.31± 0.07%) than in control healthy individuals (0.14±0.02%) (t=2.34, p<0.05).

Discussion

Absolute or relative erythropoietin depletion is considered to be the most important factor responsible for the occurrence of anemia that accompanies ESRD[4,16,29–33]. The other factors, such as a reduced RBCOR and the related RBC

TABLE 2
RED BLOOD CELL OSMOTIC RESISTANCE (RBCOR) HEMODIALYSIS TREATED PATIENTS AND HEALTHY CONTROL INDIVIDUALS

Parameter	Hemodialysis treated patients (n=58)	Healthy control individuals (N=16)	t-test	signific.
MOR (%NaCl)	0.44±0.07	0.37±0.02	6.69	**s
HSP (% NaCl)	0.52±0.09	0.44±0.02	6.23	**s
HEP (%NaCl)	0.31±0.05	0.28±0.02	3.64	**s

p<0.05; **p<0.01
MOR – middle osmotic resistance, HSP – hemolysis start point, HEP – hemolysis end point

life span are only contributing elements[1–9]. Yet, despite their position, they are the subject of intensive studies.

In our study we have attempted to establish a potential link between rHuEPO treatment and RBCOR. This is not the first attempt of the kind. However, previous researchers have not obtained identical results.

In 1991, Icardi et al.[44] investigated the effects of rHuEPO treatment on RBC mechanic fragility and deformability in HD

TABLE 3
CHARACTERISTICS OF HEMODIALYSIS TREATED PATIENTS AFTER GROUPING ACCORDING TO rHuEPO TREATMENT

	With rHuEPO	Without rHuEPO	t-test	signific.
Number of patients	29	29		
MOR (%NaCl)	0.44±0.05	0.45±0.08	0.57	ns
HSP (% NaCl)	0.50±0.07	0.53±0.09	1.42	ns
HEP (%NaCl)	0.31±0.06	0.31±0.05	0.41	ns
Age (years)	42.48±12.97	55.91±11.92	4.11	**s
HD treatment (months)	61.78±46.63	56.50±40.74	0.46	ns
Urea (mmol/l)	28.61±5.29	25.63±5.74	2.07	**s
Creatinine (μmol/l)	1009.66±235.25	941.00±199.49	1.19	ns
Potassium (mmol/l)	5.99±0.92	5.51±0.88	2.03	*s
Calcium (mmol/l)	2.46±0.18	2.51±0.18	1.06	ns
Bilirubin (μmol/l)	12.45±5.74	13.25±6.23	0.51	ns
Iron (μmol/l)	11.24±3.28	10.81±2.87	0.53	ns
Hematocrit (l/l)	0.34±0.04	0.27±0.04	6.67	**s
Reticulocytes (x 10^3 E)	11.83±8.55	13.48±4.87	0.90	ns
i-PTH (pg/ml)	213.20±230.67	238.02±233.82	0.41	ns

* $p<0.05$; **$p<0.01$, ns – not significant
MOR – middle osmotic resistance, HSP – hemolysis start point, HEP – hemolysis end point

TABLE 4
FREQUENCY OF NORMAL RED BLOOD CELL OSMOTIC RESISTANCE (RBCOR) PARAMETERS IN HEMODIALYSIS TREATED PATIENTS AFTER GROUPING ACCORDING TO rHuEPO TREATMENT

Parameter	Number of normal values			
	With rHuEPO	Without rHuEPO	Chi-square test	signific.
MOR	12	10	0.07	ns
HSP	9	8	0.00	ns
HEP	9	10	0.00	ns
Number of patients treated with calcium antagonists	12	11	0.01	ns

ns – not significant
MOR – middle osmotic resistance, HSP – hemolysis start point, HEP – hemolysis end point

and hemodiafiltration patients. In their study, both groups of patients, particularly the HD patients, showed RBC membrane damage. They found that rHuEPO considerably improved the studied properties, which they attributed to the production of new RBC. Three years later, in their study of the effects of rHuEPO treatment on the cardiovascular function, Haedersdal et al.[45] recorded a reduced RBCOR in a small HD treated group (n= 11) (although it was not possible to conclude from the results presented in the their table). They concluded that the unchanged peripheral vascular resistance, blood pressure and cardiac index were due to a reduced RBCOR, i.e. to its higher flexibility despite increased hemoglobin, hematocrit and RBC volume.

In 1995 Labonia[4] found that the substitution of L-carnitine maintained the same hematocrite level at considerably lower rHuEPO dosages in 13 hemodialysed patients with no change in RBCOR and endogenous erythropoietin concentration. The reduced rHuEPO dosage yielded the same effect only in patients receiving higher (although statistically not significant) initial rHuEPO dosages (120.3± 51.3 : 81.2±40.4 UI/kg body weight weekly) and having a higher (also not significantly) endogenous erythropoietin level (38.6±11.8 : 26.8±7.0 mU/ml). He concluded that erythropoietin resistance was due to L-carnitine deficiency.

In their examination of the relationship between serum L-carnitine and RBCOF in HD patients, Matsumara et al[3]. found no difference in RBCOF in rHuEPO treated patients and non-rHuEPO treated patients. They concluded that rHuEPO neither directly affected RBCOF, nor the related newly produced RBC.

San et al.[49] found that rHuEPO improved lipid peroxidation and intraerythrocytic antioxidative system, and that anemia correction was partly due to RBC membrane stability enhancement.

Our results are in agreement with the previous results of only several of the mentioned authors[3,4]. Namely, we were not able to prove that rHuEPO affected RBCOR either. The results meet our expectations because rHuEPO neither changes uremic plasma, nor do the rHuEPO-related RBC differ from those produced by endogenous erythropoietin.

ESRD patients do not necessarily exhibit a reduced RBCOR. Of our patients, normal MOR was found in 37.93% cases, normal HSP was detected in 29.31% cases and normal HEP was found in 32.76% cases. However, all the three parameters were normal in only 5 patients (8.62%). Docci et al.[7] found a normal RBCOR in every fifth respondent, Weiner et al[8]. in each, and Jakic et al.[9] in 87.72% of the patients.

More than 15 years ago, secondary hyperparathyroidism and parathormone were given high importance in the pathophysiology of anemia in CRF patients. Parathormone was proved to be a direct and indirect erythrocytopoiesis inhibitor, to reduce RBCOR and to shorten RBC life span[7–8,50–52]. Our study found no correlation between i-PTH and RBCOR, but a statistically significant correlation was established between MOR and serum concentrations of calcium and hydrogen ions. Docci et al[7]. did not find any correlation between RBCOR and histochemical indicators of secondary hyperparathyroidism. Matsumara et al.[3] did not find a correlation between RBCOR and serum concentrations of urea and creatinine, but only with the serum L-carnitine level. Wu et al.[2] presented a correlation between RBCOF and serum urea, parathormone and osmolality.

Based on the obtained results we conclude that rHuEPO does not affect on RBCOR in hemodialysed patients, that not all hemodialysed patients display a reduced RBCOR, and that the low number of statistically significant correlations

between RBCOR and laboratory parameters characteristic abnormal in uremic syndrome (with serum calcium and hydrogen concentrations) do not indicate with certainty their causal relationship.

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UTJECAJ LIJEČENJA ERITROPOETINOM (rHuEPO) NA OSMOTSKU REZISTENCIJU ERITROCITA

S A Ž E T A K

U bolesnika s kroničnim bubrežnim zatajenjem (KBZ) osmotska rezistencija eritrocita (ORE), sposobnost da zadrže svoj integritet, opirući se osmozi, pri izlaganju hipotoničnim otopinama natrijeva klorida, smanjena je često, ali ne uvijek. Zajedno sa smanjenom sposobnosti eritrocita da mijenjanju svoj oblik pri prolasku kroz nutritivne kapilare, dovodi do skraćenja njihovog vijeka, a tako i do nastanka anemije. Iako se vjeruje da vijek eritrocita ove skupine bolesnika uglavnom određuju izvaneritrocitni čimbenici i sami eritrociti su često predmet proučavanja. U ovom radu ispitivali smo da li humani rekombinantni eritropoetin (rHuEPO) utječe na ORE hemodijalizom liječenih bolesnika. Ispitivanjem je obuhvaćeno 58 bolesnika, prosječne dobi 49±14 godina, prosječno liječenih hemodijalizom 59±43 mjeseca. Polovica bolesnika je za korekciju anemije dobivala rHuEPO. Svakom bolesniku određena je ORE (koncentracija natrijeva klorida kod koje je zabilježena početna – HSP i završna hemoliza – HEP i koncentracija natrijeva klorida kod koje je hemoliziralo 50 % eritrocita – MOR) i niz laboratorijskih parametara karakterističnih za uremijski sindrom. Kontrolnim zdravim ispitanicima (n=16) određena je samo ORE. Prosječne vrijednosti HSP, HEP i MOR bolesnika liječenih i neliječenih rHuEPOm nisu se razlikovale. Bolesnici liječeni hemodijalizom imali su od kontrolnih ispitanika statistički značajno niže prosječne vrijednosti HSP, HEP i MOR. Nađena je samo pozitivna značajna korelacija MOR s predijaliznom razinom kalcija ($r=0,28$, $p<0,05$) i vodikovih iona ($r=0,37$, $p<0,05$). Na osnovi rezultata našeg ispitivanja zaključujemo da rHuEPO ne utječe na ORE hemodijalizom liječenih bolesnika, da smanjena ORE nije obvezan nalaz i da je u korelaciji s malim brojem laboratorijskih parametara karakterističnih za uremijski sindrom.