THE RELATIONSHIP OF INFLAMMATION MARKERS AND VASCULAR ENDOTHELIAL INDICATORS IN PROGRAM HEMODIALYSIS PATIENTS IN SODIUM DEOXYRIBONUCLEATE TREATMENT

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The aim of the investigation was to study the dynamics and relationship of inflammatory process activity indicators and vascular endothelial condition in program hemodialysis (PHD) patients, sodium deoxyribonucleate being used in complex treatment.

Materials and Methods. The study involved 69 PHD patients with end-stage renal failure. The patients were randomized into two groups. Control group patients with PHD (n=35) received background therapy, while the patients of the treatment group (n=34) — background therapy and 75 mg (5 ml of 1.5% solution) of sodium deoxyribonucleate (Derinat, Technomedservice, Russia) intramuscularly (10 injections, every 24 h).

The content of interleukin-6, -1β, -10 (IL-6, IL-1β, IL-10), tumor necrosis factor alpha (TNF-α), endothelin (1-21) and von Willebrand factor (vWF) activity were analyzed using enzyme immunoassay, stable metabolites of nitric oxide (NO) — spectrophotometrically; of C-reactive protein (CRP) — by immunoturbidimetric method; of fibrinogen — using Klaus method.

The indices were assessed within three months: on day 1 (I examination, in treatment group — before sodium deoxyribonucleate administration), day 30 (II examination), and day 90 (III examination); at each of the mentioned stages — before hemodialysis procedure. Blood serum was the object of the research.

Results. There were observed an increased content of IL-6, IL-1β, IL-10, CRP, fibrinogen, NO and endothelin (1-21), and the decrease of TNF-α and vWF activity in relation to initial data.

Sodium deoxyribonucleate as part of complex background therapy of PHD patients reduced the levels of IL-6, IL-1β, CRP (day 30) and fibrinogen (days 30 and 90), with the increase in IL-10 level (day 30) in relation to both: initial indices and control group indices. TNF-α content decreased only in relation to the initial level; and on day 30 it was higher than the similar index in the control group. We observed the lower NO level compared to the background therapy (days 30 and 90), but higher vWF activity (day 30).

PHD patients were found to have the interaction of the changes of inflammation markers and endothelial condition indices. However, in sodium deoxyribonucleate administration the range of the correlation-dependent indices changed in comparison with those in background therapy. Therefore, we recommend a follow-up of inflammatory markers and vascular endothelial condition indices if sodium deoxyribonucleate is used as part of complex therapy for PHD patients.

Key words: program hemodialysis; inflammatory markers in PHD; vascular endothelial condition in PHD; sodium deoxyribonucleate.

According to the reduction level of glomerular filtration rate, 5 stages of chronic kidney disease (CKD) are distinguished. End-stage (terminal) renal disease requires substitution therapy: kidney transplantation, hemodialysis, or peritoneal dialysis. Over 85% patients with V stage disease undergo program hemodialysis (PHD) [1].

PHD patients have high rate of cardiovascular pathology, which causes at least one third of all admissions to hospital and half of lethal outcomes. And the risk of cardiovascular pathology in dialysis patients exceeds the risk in general population by 10–20 times [2]. It is due to the fact that dialysis patients are exposed to both: traditional risk factors (arterial hypertension, overweight, dyslipidemia, left ventricular hypertrophy), and also numerous additional risk factors including those related to uremia and dialysis (endothelial dysfunction, oxidative stress, anemia, calcium phosphoric imbalance and systemic inflammatory reaction) [3].

Moreover, PHD patients are found to have a high rate of infectious complications, which rank second among other death causes in dialysis patients [4]. Infections related to vascular access cause the development of systemic inflammatory reaction in PHD. Persistent

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infections, reduced renal clearance of cytokines, the accumulation of low molecular weight uremic toxins, an atherosclerotic process, chronic heart failure, biological incompatibility of dialysis membranes, inverse filtering and complement system activation make a certain contribution to systemic inflammation development in this group patients [5].

Systemic inflammatory reaction, in its turn, is one of the factors causing vascular endothelial dysfunction in PHD patients. In literature there are reports on the correlation of vascular wall damage degree, endothelial dysfunction, and atherosclerosis development in PHD patients if TNF-α, IL-1β, IL-6 and CRP levels are increasing [6]. Therefore, medical correction aimed at decreasing chronic inflammatory process activity and improving endothelial condition is the necessary condition to reduce the risk of cardiovascular diseases in dialysis patients.

Sodium deoxyribonucleate (Derinat) has a broad spectrum of pharmacological activity including an immunomodulatory effect at cell and humoral levels, and a radioprotective effect, also it stimulates regeneration, has an anti-inflammatory, anti-tumor and low anticoagulant effect, improves the condition of tissues and organs in vascular dystrophies, regulates hemopoiesis. As part of complex therapy of coronary heart disease, it improves myocardial contractility, prevents myocite death, improves microcirculation in cardiac muscle, and increases physical load tolerance [7, 8]. In addition, the effect of sodium deoxyribonucleate on the dynamics of indices characterizing the inflammatory process activity and endothelial condition, as well as the dependence of these changes in PHD patients have not been studied until now.

The aim of the investigation was to study the dynamics and relationship of inflammatory process activity indicators and vascular endothelial condition in program hemodialysis patients, sodium deoxyribonucleate being used in complex treatment.

Materials and Methods. The studies were carried out using clinical base of Fespharm Company and laboratory facilities of Nizhny Novgorod Regional Clinical Diagnostic Centre. The study involved 69 patients with end-stage renal disease; they were referred to PHD by Nizhny Novgorod Regional Dialysis Committee. Inclusion criteria were the following: chronic end-stage renal failure, program hemodialysis at least for 6 months, coronary heart disease (stable effort angina, II functional class), dyslipidemia, age: 35–70 years, hemoglobin level ⩾100 g/L, hemodialysis adequacy indicators: URR⩾65%, Kt/V⩾1.2. Exclusion criteria were as follows: diabetes mellitus, rheumatoid arthritis.

The patients were divided into two groups by simple random. Control group patients (n=35, among them 23 male and 12 female patients) were on PHD and received background therapy only. The treatment group of PHD patients (n=34) received background therapy and were given sodium deoxyribonucleate (Derinat, Technomedservice, Russia): 75 mg (5 ml of 1.5% solution) intramuscularly (10 injections, every 24 h).

Mean age of patients in the control group was 55.51±1.31 years, in the treatment group — 54.62±0.76 years. The disease duration from the moment of renal disease detection to chronic kidney disease revealed was 10.44±0.91 and 9.74±0.44 years, and from the moment of chronic kidney disease revealed to hemodialysis initiation — 3.33±0.31 and 4.63±1.18 years, respectively. No significant differences in the indices mentioned between the groups were found.

The study complies with the declaration of Helsinki (adopted in June, 1964 (Helsinki, Finland) and revised in October, 2000 (Edinburg, Scotland)) and approved by the Ethics Committee of Nizhny Novgorod State Medical Academy. Written informed consent was obtained from all patients.

Chronic program hemodialysis procedures were carried out 3 times a week for 4–5 h on Innova apparatuses (Gambro, Italy). Mean true dialysis time in control group patients was 13.82±0.16, in treatment group patients — 13.81±0.14 h a week.

Background therapy in both groups included iron preparation — iron (III) hydroxide sucrose complex (Venofer, Vifor, Switzerland) by 5 ml (elementary ferrum, 100 mg) by slow venous stream infusion, after hemodialysis procedure, 2 times a month; erythropoietin (Erythrostim, Microgen, Russia) by 2000 ME by venous stream perfusion, after hemodialysis procedure, 1–3 times a week (under hemoglobin level control); anticoagulant — heparin sodium (Belmedpreparaty, Belarus) by 5000–12 500 U intravenously, during every hemodialysis procedure, as well as the preparations for background therapy of coronary heart disease (beta-adrenoreceptor blocking agents — metoprolol, bisoprolol and an antiplatelet preparation — acetylsalicylic acid).

The content of interleukins (IL-6, IL-1β, IL-10), TNF-α was studied by enzyme immunoassay on an IEA-analyzer EFOS 9305 (Sapfir, Russia). CRP level was determined by an immunoturbidimetric method on a Stat Fax 1904+ semi-automatic biochemical analyzer (USA) using assay kit (C-reactive protein-Novo, Vector Best, Russia). Fibrinogen concentration was measured by Klaus method on a Thrombostat-1 coagulometer (Behnk Elektronik, Germany).

Endothelin level (1-21) and von Willebrand factor (vWF) activity were studied by enzyme immunoassay on an IEA-analyzer EFOS 9305 (Sapfir, Russia), the content of stable nitric oxide (NO) metabolites — spectrophotometrically on a APEL PD 303 spectrophotometer (Japan).

The mentioned indices were assessed within three months: on day 1 (examination I — initial values, in treatment group — before sodium deoxyribonucleate administration), on day 30 (examination II) and day 90

(examination III), at each stage — before hemodialysis. Blood serum was the object of the research.

The data were statistically processed using statistics package STADIA 7.0/prof and Microsoft Excel. The statistical significance level of the differences between the samplings with distribution, being no different from the norm, was determined using Student t-test and Fisher's test; between paired samples having distribution different form the norm — using Wilcoxon signed rank test; between independent samples with non-normal distribution — using Wilcoxon test and Van der Waerden test. The findings were processed using a nonparametric correlation technique (Spearman and Kendall coefficients).

The results are presented as M±m, where M — an arithmetical mean, m — a standard error of the mean.

Results. The dynamics of the content of inflammation markers in blood serum of the patients under study was characterized by decreased TNF-α content compared to the first examination results: by day 30 in the treatment group — by 14.49% ($p<0.001$), in the control group — by 64.80% ($p<0.001$), by day 90 — by 52.90% ($p<0.001$) and 53.43% ($p<0.001$), respectively. Moreover, by day 30, TNF-α level after sodium deoxyribonucleate administration significantly exceeded that in the control group ($p<0.001$) (Table 1).

Moreover, when sodium deoxyribonucleate was administered, by day 30 there was the decrease of IL-6 by 82.32% ($p<0.001$), while in the control group this index increased by 12.53% ($p<0.05$) in relation to the initial value. The differences in the dynamics of the index in the treatment group were significant ($p<0.001$). By 90 day, IL-6 content increased in relation to the initial level in both groups (by 72.73% — in the treatment group and by 76.73% — in the control group) with no significant differences between the groups.

Similar changes were revealed when analyzing IL-1β level: the decrease by 45.16% ($p<0.001$) in relation to the initial value by day 30 after a course of sodium deoxyribonucleate with the increase of this index in the control group by 17.60% ($p<0.05$) ($p<0.001$ between the changes of the index in two groups under study), as well as its increase in relation to the initial value in patients of both groups (by 17 times, $p<0.001$) by day 90, without significant differences between the groups.

Simultaneously, by day 30 the increase in IL-10 in relation to the initial value was recorded: in the treatment group — by 23 times ($p<0.001$), in the control group — by 10 times ($p<0.001$). It should be noted that IL-10 level after a course of sodium deoxyribonucleate by day 30 significantly exceeded that in the control group ($p<0.001$). By day 90 the indices of both groups were compared, its increase by 19 times in relation to the initial value being recorded, $p<0.001$ (See Table 1).

After a course of sodium deoxyribonucleate, by day 30 there was recorded CRP content decrease by 47.67% ($p<0.001$) in relation to the examination I findings, while in the control group there was the tendency for its increase ($p<0.001$ between the changes of this index in the treatment group and in the control group). By day 90 CRP content was found to increase slightly in relation to the initial level in patients of both groups with no significant differences between the patients under study.

In the treatment group by day 30 there was the decrease of fibrinogen level by 16.87% ($p<0.001$) in relation to the initial level, while in the control group this index changed insignificantly ($p<0.001$ between the changes of this index in the treatment group and in the control group). By day 90 the dynamics of this index in the treatment group and in the control group differed significantly as well — after a course of sodium deoxyribonucleate, fibrinogen level was found to decrease by 14.29% ($p<0.001$) in relation to the examination I data, while in the control group, in contrast, it increased by 7.03% ($p<0.01$) (See Table 1).

After a course of sodium deoxyribonucleate the patients were recorded to have unidirectional (with the control group) dynamics of NO content — the increase in relation to the initial level by day 30 by 28.13% ($p<0.01$) and the tendency for increase by day 90 (in the control group — the increase by 64.90 and 25.21%, respectively,

Table 1

Dynamics of inflammation markers (M±m)

Index	Stage	Treatment group	Control group
TNF-α, pg/ml	Examination I	5.52±0.38	5.54±0.54
	II (day 30)	4.72±0.25; $p_{1,c}<0.001$	1.95±0.22; $p_1<0.001$
	III (day 90)	2.60±0.28; $p_1<0.001$	2.58±0.28; $p_1<0.001$
IL-6, pg/ml	Examination I	3.96±0.52	3.91±0.50
	II (day 30)	0.70±0.08; $p_{1,c}<0.001$	4.40±0.55; $p_1<0.05$
	III (day 90)	6.84±0.54; $p_1<0.001$	6.91±0.65; $p_1<0.001$
IL-1β, pg/ml	Examination I	1.24±0.16	1.25±0.16
	II (day 30)	0.68±0.13; $p_{1,c}<0.001$	1.47±0.07; $p_1<0.05$
	III (day 90)	20.99±1.63; $p_1<0.001$	21.06±1.58; $p_1<0.001$
IL-10, pg/ml	Examination I	0.27±0.10	0.27±0.10
	II (day 30)	6.25±0.31; $p_{1,c}<0.001$	2.76±0.28; $p_1<0.001$
	III (day 90)	5.0±0.44; $p_1<0.001$	5.03±0.43; $p_1<0.001$
CRP, mg/L	Examination I	41.45±0.66	41.40±0.64
	II (day 30)	21.69±0.91; $p_{1,c}<0.001$	41.83±0.63
	III (day 90)	43.49±1.10	43.42±1.07
Fibrinogen, g/L	Examination I	4.27±0.11	4.27±0.10
	II (day 30)	3.55±0.10; $p_{1,c}<0.001$	4.39±0.14
	III (day 90)	3.66±0.11; $p_{1,c}<0.001$	4.57±0.13; $p_1<0.01$

Note: p_1 — the significance level of differences with examination I; p_c — with the control group.

Table 2

Dynamics of endothelial state indices (M±m)

Index	Stage	Treatment group	Control group
NO, μmol/L	Examination I	7.18±0.55	7.18±0.36
	II (day 30)	9.20±0.83 $p_1<0.01$; $p_c<0.001$	11.84±0.70 $p_1<0.001$
	III (day 90)	7.27±0.55; $p_c<0.001$	8.99±0.35; $p_1<0.001$
Endothelin (1-21), fmol/ml	Examination I	0.97±0.15	0.97±0.10
	II (day 30)	2.19±0.30; $p_1<0.001$	1.99±0.14; $p_1<0.001$
	III (day 90)	1.63±0.08; $p_1<0.001$	1.65±0.08; $p_1<0.001$
vWF, %	Examination I	161.20±5.49	161.10±5.47
	II (day 30)	148.00±4.22 $p_1<0.01$; $p_c<0.05$	135.30±3.84; $p_1<0.001$
	III (day 90)	139.40±3.92 $p_1<0.001$	135.50±3.69 $p_1<0.001$

Note: p_1 — the significance level of differences with examination I; p_c — with the control group.

p<0.001). It should be noted that NO content increase in patients of the treatment group during the whole observation period was less marked than in the control group (p<0.001), moreover, NO level in the treatment group patients remained lower than that in the control group at both stages (p<0.001) (Table 2).

Endothelin level (1-21) in patients of both groups also grew compared to the initial value: by day 30 — by 2 times (p<0.001), by day 90 — by 68.04% (p<0.001) and 70.10% (p<0.001) in the treatment group and in the control group, respectively.

In addition, after a course of sodium deoxyribonucleate the patients were recorded to have unidirectional vWF activity dynamics, though less marked than in the control group. So, on day 30 vWF activity decrease in the treatment group patients was 8.19% (p<0.01 regarding the examination I findings), in the control group — 16.01% (p<0.001) (p<0.05 between the groups); on day 90 — 13.52% (p<0.001) and 15.89% (p<0.001), respectively. However, vWF activity in patients of the treatment group on day 30 remained higher than in the control group (p<0.05) (See Table 2).

The correlation analysis carried out showed that during the observation period the control group patients had a direct correlation between level changes of IL-1β and endothelin (1-21) (r=0.57; p<0.001), IL-6 and NO (r=0.34; p<0.05), CRP and NO (r=0.40; p<0.01), as well as an inverse correlation between the changes of the content of IL-1β and vWF activity (r=–0.28; p<0.05), IL-6 level and vWF activity (r=–0.35; p<0.05).

When sodium deoxyribonucleate was used as part of a complex background therapy of PHD patients there was the direct correlation between the changes of IL-1β and endothelin (1-21) content (r=0.33; p<0.05), IL-6 and endotelin (1-21) (r=–0.46; p<0.01), IL-10 and NO (r=0.43; p<0.01). Moreover, the inverse correlation was recorded between the changes of IL-6 level and vWF activity (r=–0.37; p<0.05).

Discussion. The analysis of the study findings suggests that during the observation period the background therapy of PHD patients appeared to be characterized by the increase in the content of such inflammatory markers as IL-6, IL-1β, IL-10, CRP, fibrinogen at decreased TNF-α level in relation to the results of the background examination. The increase of IL-6, IL-1β, CRP and fibrinogen levels can be considered as the manifestation of systemic inflammatory reaction [9, 10]. It has been proved that the higher plasma levels of inflammatory markers (CRP, TNF-α, IL-1β, IL-6 and fibrinogen) in patients with chronic kidney disease, the severer the disease [11].

IL-10 level increase is a positive moment since this cytokine has anti-inflammatory properties [12], maintains normal adult kidney functions: modulates normal parameters of anatomical structure of a malpighian glomerulus and its functions [13], though the increase of IL-10 level in blood serum is not characteristic for chronic processes including PHD patients with V stage chronic kidney disease [14].

In addition, against the background therapy of the examined patients within the observation period there was the growth of NO and endothelin (1-21) content as well as the decrease of vWF activity. The increase of endothelin level is an important marker of endothelial dysfunction and one of potential reasons of NO concentration growth since endothelin increases NO synthesis through endothelin B_1-receptors [15].

Sodium deoxyribonucleate as part of a complex background therapy of PHD patients reduces IL-6, IL-1β, CRP levels (day 30) and fibrinogen level (day 30 and day 90) increasing IL-10 level (day 30) in relation not only to the initial value but also to the control group that indicates the reduced intensity of the inflammatory process in the patients of the studied group. The mentioned changes can be explained by an anti-inflammatory effect of sodium deoxyribonucleate [16]. The ability of sodium deoxyribonucleate to reduce fibrinogen levels has been also proved by other researchers [7, 17]. It should be noted that TNF-α content decreases in relation to the initial level only, on day 30 it remaining higher than that in the control group.

The dynamics of the endothelial state indices under study is unidirectional with that in the control group. And sodium deoxyribonucleate provides the lower NO level (days 30 and 90) compared to the background therapy, and higher vWF activity (day 30).

The correlation analysis findings suggest the dialysis patients during 90 days of the observation period against

the background therapy to have the correlation of such indices of endothelial condition as NO level (with the levels of inflammatory mediators IL-6 and CRP), endothelin (1-21) (with IL-1β level), and vWF activity (with IL-1β and IL-6 levels). It can be due to the fact that endothelial cells are target cells of some cytokines, IL-1β and IL-6 in particular [18].

After a course of sodium deoxyribonucleate as part of a complex background therapy of PHD patients there was the correlation of the levels of NO and IL-10; endothelin (1-21) and IL-1β, IL-6; vWF activity and IL-6 content. It indicates that sodium deoxyribonucleate changes the range of indices, which are in correlation dependence compared to the background therapy.

Conclusion. A course of sodium deoxyribonucleate (Derinat) as part of a complex therapy of PHD patients with end-stage renal failure enables to reduce the content of IL-6, IL-1β, CRP (by day 30 of observation), fibrinogen (by day 30 and day 90), increase IL-10 level (by day 30), as well as provide higher TNF-α level (by day 30).

An endotheliotropic effect of sodium deoxyribonucleate is shown by lower NO level (day 30 and day 90) compared to the background therapy, but higher vWF activity (day 30).

When sodium deoxyribonucleate is used, the spectrum of the indices studied, which are in correlation dependence, changes compared to the spectrum when the background therapy is used only. Therefore, if sodium deoxyribonucleate is used as part of a complex background therapy of program hemodialysis patients, we recommend a dynamic control of inflammatory markers and indices of endothelium condition.

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