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Analysis of hemodynamic parameters and quality of life in patients with chronic kidney disease and arterial hypertension

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ABSTRACT

Purpose. The work is devoted to study the effects of antihypertensive, lipid-lowering and metabolic therapy in office and the average hemodynamic parameters, the parameters of central pressure in the aorta, vascular wall stiffness and quality of life in patients with CKD stage 3 in combination with arterial hypertension of 1-2 degrees, and without it. **Materials and methods.** Were examined patients with arterial hypertension of 1-2 degrees and CKD stage 3. Measured hemodynamic parameters with the help of a daily BP monitor "BPLab". The quality of life of patients was assessed by the questionnaire MOS SF36. **Results.** The greatest changes in the indicators of central hemodynamics and vascular stiffness were noted in the group of patients with comorbidity. **Conclusion.** The combination of antihypertensive therapy (losartan and diltiazem) with meldonium and rosuvastatin significantly decreases indices of central and peripheral hemodynamics and vascular stiffness. Add meldonium part of therapy significantly improves the quality of life of patients.

KEY WORDS: antihypertensive therapy; arterial hypertension; central aortic pressure; chronic kidney disease; hemodynamic parameters; vascular stiffness.

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Análisis de parámetros hemodinámicos y de calidad de vida en pacientes con enfermedad renal crónica e hipertensión arterial

RESUMEN

Propósito. En el trabajo se estudian los efectos de la terapia antihipertensiva, hipolipemiante y metabólica en el consultorio y los parámetros hemodinámicos medios, los parámetros de presión central en la aorta, rigidez de la pared vascular y calidad de vida en pacientes con ERC estadio 3, en combinación con hipertensión arterial de 1-2 grados, y sin ella. Materiales y métodos. Se examinaron pacientes con hipertensión arterial de 1-2 grados y ERC en estadio 3. Se midieron los parámetros hemodinámicos con la ayuda de un monitor de PA diario "BPLab". La calidad de vida de los pacientes se evaluó mediante el cuestionario MOS SF36. Resultados. Los mayores cambios en los indicadores de hemodinámica central y rigidez vascular se observaron en el grupo de pacientes con comorbilidad. Conclusión. La combinación de terapia antihipertensiva (losartán y diltiazem) con meldonium y rosuvastatina disminuye significativamente los índices de hemodinámica central y periférica y rigidez vascular. Agregar meldonium como parte de la terapia mejora significativamente la calidad de vida de los pacientes.

PALABRAS CLAVE: terapia antihipertensiva; hipertensión arterial; presión aórtica central; enfermedad renal crónica; parámetros hemodinámicos; rigidez vascular.

Introduction

Ensuring the greatest possible reduction in the risk of cardiovascular complications, which involves not only normalizing the level of blood pressure (BP), but also correcting all modifiable risk factors, preventing or ensuring the reverse development of target organ damage, and treating associated clinical conditions, is the main goal of controlling blood pressure.

Damage to the kidneys as target organs in hypertension (AH) has attracted the attention of a large number of researchers in recent years (Williams et al., 2018; Matsushita et al., 2010). It has been proven that there is a high incidence of a combination of chronic kidney disease (CKD) with hypertension, chronic heart failure, and diabetes mellitus (The Committee of experts of the Russian society of cardiology et al., 2014; Smirnov et al., 2012; Nedogoda, 2005).

Kidney disease is the most common cause of secondary AH. According to various authors, hypertension at various stages of development of chronic kidney disease is observed in 85-100 % of cases. In the structure of complications of CKD, especially in

chronic renal failure (CRF), the AH syndrome occupies one of the leading places regardless of etiological factors. There are close pathophysiological correlations between hypertension and the functional state of the kidneys. Thus, impaired renal function, consisting in insufficient excretion of sodium and water, is considered the most important pathogenetic link in increasing BP. Hypertension contributes to kidney damage due to vasoconstriction, structural changes in the renal arterioles, and parenchymal ischemia (Matsushita, K., van der Velde, M., Astor, B.C. et al., 2010).

The existing evidence base for the use of meldonium (Mildronate) in clinical practice indicates the multifaceted effect of the drug in coronary heart disease. Carnitine-dependent and carnitine-independent mechanisms of action provide the antianginal, anti-ischemic and vasoprotective effect of meldonium with stable angina pectoris and chronic heart failure. Additional properties have been identified that determine the structurally modifying effect on the myocardium, antiarrhythmic, improving carbohydrate and lipid metabolism (Trisvetova E.L., 2019).

However, the literature does not adequately cover the issues related to the development of CKD in young patients with hypertension of 1–2 degrees, and the factors affecting the development of CKD in these patients have not been studied.

To assess the effect of various antihypertensive therapy (AHT) options on the clinical outcomes of AH, in recent years they began to consider their effect on the parameters of central aortic pressure (CAP) and reflected wave index (augmentation index - IA) (Ivanov et al., 2008; Kobalava and Kotovskaya, 2015; Nedogoda and Chalyabi, 2006; Martynov, 2007; Olejnikov et al., 2009; Pshenicin and Mazur, 2007; Gosse et al., 2005). Antihypertensive drugs differently affect both the nature of the pulse wave and the parameters of central hemodynamics, despite the same ability to lower blood pressure in the brachial artery (Rogoza et al., 2008; Chen et al., 1997; Laurent et al., 2006).

Objective: to study the effect of antihypertensive, lipid-lowering, and metabolic therapy on office and average daily hemodynamic parameters, CAP parameters, vascular wall stiffness and quality of life (QOL) in patients with stage 3 CKD, both in combination with and without grade 1-2 hypertension.

1. Material and methods

The object of the study was patients treated in the nephrology and cardiology departments of the Republican Clinical Hospital of the Kabardino-Balkarian Republic, as well as outpatients who were observed in polyclinics of the city of Nalchik. The criteria for inclusion of the patient in group 1 were as follows: the presence of CKD C3 (eGFR 30-60 ml / min) in combination with AH of the 1st and 2nd degree, age from 45 to 72 years, duration of AH no more than 10 years, lack of regular AHT. The criteria for inclusion of the patient in group 2 were as follows: the presence of AH of the 1st and 2nd degree, age from 45 to 72 years, the duration of AH no more than 10 years, the absence of regular AHT. The criteria for inclusion of the patient in group 3 were as follows: the presence of CKD C3 (eGFR 30-60 ml / min), age from 45 to 72 years. For the control group, patients were selected who, according to the examination (general clinical examination, biochemical blood test, special (interrogative), statistical, as well as comparative and system analysis methods) were found to be healthy.

The first group consisted of 45 patients with CKD C3 (eGFR 30-60 ml / min) in combination with hypertension of 1-2 degrees (average age 60 ± 9 years). The group consists of 19 men and 26 women. The second group consisted of 45 patients with AH of 1-2 degrees without CKD. The third group consisted of 45 patients with CKD C3 without hypertension. The fourth (control) group consisted of 30 clinically healthy individuals. All formed groups were comparable by age and gender.

Office hemodynamic parameters and average daily parameters of CDA were measured using the BPLab daily blood pressure monitor with an expanded version of the BPLab Vasotens and BPLab Vasotens office software by Petr Telegin (Russia) before treatment and after 8 weeks of treatment.

QOL of patients was assessed using the MOS SF36 questionnaire before treatment and within 8 weeks after treatment. The following indicators were calculated: physical health (PH), which includes physical activity (PA), role-based physical functioning (PF), physical pain (PP), and general health (GH); Mental health (MH): vitality (V), social activity (SA), role-playing emotional functioning (EF), as well as a comparison of patients' well-being (WB).

Statistical processing was performed using the Statistica 10.0 application package. The arithmetic mean and standard deviations of the studied values and the

representativeness errors were calculated. The normal distribution of the obtained data was presented in the form M ± m, where M is the arithmetic mean of the studied quantities, m is the error of representativeness. The difference in indicators in the groups was evaluated by t-student test. The significance level of the difference p = 0.05 was considered critical.

2. Research results and discussion

The clinical characteristics of the examined patients and the received therapy are presented in tables 1 and 2.

Table 1. Clinical and demographic characteristics of the examined patients

Indicator	1st group (CKD III + AH) n = 45	2nd group (AH) n = 45	3rd group (CKD III) n = 45	4th group (healthy) n = 30
Average age, years	60±9	62±10	60±9	59±11
Men, n (%)	19 (42)	22 (49)	20 (44)	14 (46)
Women, n (%)	26 (58)	23 (51)	25 (56)	16 (54)
Smokers, n (%)	11 (24) *	11 (24) *	12 (27) *	0 (0)
AH, n (%)	45 (100) *	45 (100) *	0 (0)	0 (0)
1 degree, n (%)	20 (44) *	21 (47) *	0 (0)	0 (0)
2 degrees, n (%)	25 (56) *	24 (53) *	0 (0)	0 (0)
CHF (1-2 FC according to NYHA), n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Potassium, meq / L	4,8±0,85**	4,8±0,57*	4,9±0,88**	4,2±0,44
Sodium, meq / L	143±3,29	136±3,35	142±2,84	138±3,12
Uric Acid, µmol / L	444±89	342±85	374±87	272±91
Hemoglobin level. g / l	137±23	138±16	136±24	137±15
Hematocrit%	38,94±5,83	41,83±5,14	39,48±6,60	41,18±4,16
Blood creatinine, mg / dl	1,47±0,43*	0,88±0,11	1,38±0,37*	0,73±0,17
Serum Albumin, g / l	37±6,4	41±5,1	39±5,5	42±5,4
Albuminuria, mg / day	8,4±3,1 *	3,46±0,7	7,3±2,7 *	3,08± 0,7
Left ventricular hypertrophy, n (%)	10 (22) *	8 (18) *	0 (0)	0 (0)

Glomerular filtration rate according to CKD-EPI, ml / min / 1.73 m2	47,5±11,1**	75,4±7,5	45,9±11,7**	106,8±14,5
Scale CHA2DS2-VASc, points	5±1*	3±1	2±1	2±1
Hyperlipidemia, n (%)	45 (100) *	45 (100) *	45 (100) *	0 (0)
Total cholesterol, mmol / l	5,84±0,9*	5,91±0,8*	5,92±1,0*	3,8±0,5
Low density lipoprotein cholesterol, mmol / L	3,323±0,6	3,05±0,7	3,24±0,6	2,1±0,6
High density lipoprotein cholesterol, mmol / L	1,1±0,5	1,2±0,6	1,1±0,5	1,9±0,4
Triglycerides, mmol / L	1,6±0,6	1,7±0,6	1,6±0,5	1,9±1,2

Note: * - $p < 0.05$, ** - $p < 0.01$, *** - $p < 0.001$ - in comparison with the control group

Table 2. Types of pharmacotherapy in the examined patients

Groups	Received therapy
1 (CKD III + AH), **n = 45**	1. Losartan # 100 mg in the morning at 8.00 2. Diltiazem ## 180 mg 1 time per day 3. Rosuvastatin ### 10 mg in the evening at 20.00 4. Meldonium #### 500 mg 2 times a day at 8.00 and at 14.00
2 (AH), **n = 45**	1. Losartan 100 mg in the morning at 8.00 2. Diltiazem 180 mg once daily 3. Rosuvastatin 10 mg in the evening at 20.00 4. Meldonium 500 mg 2 times a day at 8.00 and at 14.00
3 (CKD III), **n = 45**	1. Rosuvastatin 10 mg in the evening at 20.00 2. Meldonium 500 mg 2 times a day at 8.00 and at 14.00

Blocktran, Pharmstandard-Leksredstva OJSC, Russia

Diltiazem Lannacher retard, "Lannacher Heilmittel GmbH", Austria

Akorta, Pharmstandard-Tomskkhimfarm OJSC, Russia

Mildronat, JSC "Grindeks", Latvia

Information about the patients of the studied groups obtained by monitoring office hemodynamic parameters before and after treatment are presented in table 3.

From the results of the study it can be seen that the initial office hemodynamic parameters studied in all patients in the groups were higher than those of the average daily.

Based on the data obtained, it is seen that the largest changes in office hemodynamic parameters and vascular stiffness parameters (SBP on the arm, SBP on the ankle, DBP, MAP, PBP, HR, PWP, PWVao, AIx, dPdt, SAI, CAVIa) were noted in the group of patients with combined pathology - CKD and hypertension (table. 3).

The smallest deviations from the reference indicators were observed in the group of patients with CAP without hypertension. It is noteworthy that this group of patients initially also had an increase in the values of office hemodynamics and vascular stiffness, such as: SBP on the arm, SBP on the ankle, DBP, MAP, PBP, PWP, PWVao, AIx, dPdt, SAI, CAVIa) as well as the daily parameters of CDA (SAPao, MAPao, PBPao, AIx (Table 4). This indicates the presence of close cardiorenal relationships, which are reflected not only by morphofunctional impairment of renal regulation, but also by the presence of hemodynamic disorders and arterial endothelial dysfunction, mainly manifested by an increase their vascular.

When analyzing the daily indices of central hemodynamics, it is seen that the largest changes in CAP indices (SAPao, DBPao, MAPao, PBPao, Aix) were noted in the group of patients with combined pathology - CKD and hypertension (Table 4).

In the group of patients with CKD without hypertension, a significant increase in the values of some indicators of central hemodynamics, such as: SAPao, PBPao, AIx, was initially observed (Table 4).

Table 3. Dynamics of office hemodynamic parameters in combination therapy

Indicator		1st group (CKD + AH) n = 45	2nd group (AH) n = 45	3rd group (CKD) n = 45	4th group (healthy) n = 30
SBP, mmHg (Arm)	Originally	152,3±5,72***	148,4±4,24**	132,1±5,47*	113,4±3,52
	After treatment	134,2 ±4,82*#	129,5± 4,25*#	124,2±2,63	
SBP, mmHg (Ankle)	Originally	179,8±4,57***	168,3±3,59***	153,5±4,11*	141,7±3,47
	After treatment	159,5±4,06*##	153,6±3,94*#	148,6±3,73	
DBP, mmHg	Originally	89,2±3,83**	85,8±3,73*	78.4±2,92*	70,2±3,27
	After treatment	78±2,73*#	73±3,04#	71,2±2,74	

MAP, mmHg	Originally	139,6±4,91**	136,4±2,53**	124,7±2,22*	110,5±2,82
	After treatment	121,4±2,01*##	116,8±2,81##	121,1±3,02	
PBP, mmHg	Originally	72,3±4,74**	68,6±3,53**	48±2,35*	39±3,23
	After treatment	52,5±2,63*##	47,2±2,92##	43,8±2,19	
HR, bpm	Originally	82,4±3,13**	76,5±2,89*	71,6±2,32	69±2,04
	After treatment	76,2±2,04*#	74,6±2,15	70,2±1,96	
PTT, ms	Originally	159,3±4,63***	149±4,74***	131,1±3,18**	117,7±2,74
	After treatment	132,8±3,83*##	123,8±3,25###	120,2±2,93#	
PWVao, m / s	Originally	19,2±1,92**	17,5±1,77**	12,3±1,41*	7,2±1,82
	After treatment	10,3±1,81##	9,6±1,64#	8,8±1,5	
AIx, %	Originally	44,7±4,73***	38,5±3,26**	28,8±3,69*	18,5±2,83
	After	25,2±3,92##	23,6±3,51##	21,7±3,12	
dPdt, mmHg / s	Originally	1090,74±92,14***	892,85±69,95***	525,52±45,25**	336,46±22,36
	After treatment	809,75±68,15***#	683,58±55,27**#	425,24±53,41#	
SAI, mmHg	Originally	25,3±2,52***	19,7±1,51***	9,21±1,08*	4,9±1,7
	After treatment	9,2±2,25##	7,8±1,14##	5,8±1,13#	
CAVia	Originally	28,19±2,36***	26,11±2,02**	23,4±2,43*	15,2±1,47
		24,62±1,74*#	22,93±2,61*	18,3±1,62	

Note: SBP - systolic blood pressure, DBP - diastolic blood pressure,

MAP - mean arterial pressure, PBP - Pulse arterial pressure,

HR - heart rate, PWP - pulse wave propagation time,

PWVao - pulse wave velocity, AIx - augmentation index,

dPdt is the rate of increase in blood pressure, SAI is the systolic area index,

CAVIa - cardio-ankle vascular index,

* - the differences are significant in relation to the indicators of the healthy comparison group (p<0.05),

** - p ‹0.01,

*** - p ‹0.001;

- the differences are significant in relation to the initial indicators (p<0.05),

- p ‹0.01, ### - p ‹0.001

Table 4. The dynamics of the daily values of CDA in combination therapy

CDA indicators	1 group (CKD + AH)	2 group (AH)	3 group (CKD)	4 group (healthy)
SAPao, mmHg - before treatment / after treatment	139,6±5,29*/ 121,5±2,23##	135,9±2,22*/ 117,5±2,64###	125,1±2,23*/ 120,9±3,17	110,4±2,37
DBPao, mmHg - before treatment / after treatment	81,7±3,82*/ 73,4±1,73#	79,3±1,70*/ 72,5±1,12##	76,4±1,78/ 75,8±1,35	73,1±0,78
MAPao, mmHg - before treatment / after treatment	105,8±5,73**/ 88,5±1,69##	100,1±3,45*/ 84,3±2,37##	86,4±2,35/ 85,7±1,89	83,4±1,12
PBPao, mmHg - before treatment / after treatment	67,3±4,09***/ 44,7±1,61###	60,7±3,65***/ 41,3±1,92###	45,3±1,68*/ 40,9±1,16#	37,7±1,36
Aortic Augmentation Index (AIx),% - before treatment - before treatment / after treatment	36,6±4,41***/ 20,2±2,13##	27,7±3,52**/ 19,4±1,65#	23,3±2,09*/ 20,3±2,15	16,1±1,22
Aortic augmentation index (AIx,%, reduced to HR = 75 bpm - before treatment / after treatment	32,6±4,44**/ 21,2±2,72#	27,4±3,21**/ 20,7±3,62#	23,2±2,06*/ 21,3±2,76	17,6±1,86

Note: SAPao - systolic aortic arterial pressure; DBPao - diastolic aortic blood pressure; MAPao - mean aortic arterial pressure; PBPao - central pulse blood pressure; Aix - aortic augmentation index;

* - the differences are significant in relation to the indices of the healthy comparison group (p<0.05), ** - p ‹0.01, *** - p ‹0.001; # - differences are significant in relation to the initial indicators (p<0.05), ## - p ‹0.01, ### - p ‹0.001

Against the background of combined antihypertensive, lipid-correcting and metabolic therapy in patients of the 1st and 2nd groups, a significant decrease in the indices of central and peripheral hemodynamics was noted (Table 3, Table 4).

A group of patients with CKD without hypertension (group 3) who received lipid-lowering and metabolic therapy (rosuvastatin and meldonium, respectively) during treatment experienced a decrease in both office hemodynamics and vascular stiffness (SBP

on the arm, SBP on the ankle, DBP, MAP, PBP, PWP, PWVao, AIx, dPdt, SAI, CAVIa), as well as initially increased daily CAP parameters (SAPao, PBPao, AIx) (Table 3, Table 4). However, significant changes during treatment were observed only in the parameters of the pulse wave propagation time (PWP), the rate of increase in blood pressure (dPdt), the systolic area index (SAI) (Table 3), as well as in terms of the central pulse blood pressure (PBPao) (table 4).

Indicators QOL in patients of the 1st, 2nd and 3rd groups were initially comparable. An analysis of QOL indices revealed a reliable, statistically significant improvement in QOL in patients of the 1st and 2nd groups according to the following scales: physical functioning, vital activity, social functioning, role-based emotional functioning, mental health, as well as the psychological component of health (Fig. 1a, 1b).

In patients of the 3rd group, significant improvement was noted only on the scales of physical health, while on the scales characterizing mental health, the observed positive dynamics was unreliable (Fig. 1c).

The results of the study showed that a more significant dynamics of QOL indicators was observed in patients of the 1st and 2nd groups, who received meldonium at a dose of 1000 mg per day along with AHT (Figs. 1a, 1b).

Conclusions

Thus, the initial office studied hemodynamic parameters in all patients in the groups were higher than those of the average daily. In patients with stage 3 CKD, according to the study of daily monitoring of blood pressure, elevated indicators of central and peripheral hemodynamics are detected. An increase in both office hemodynamic parameters and CAP parameters, stiffness, and a decrease in arterial bed elasticity are most pronounced in patients with stage 3 CKD in combination with hypertension. The combination of AHT (losartan and diltiazem) with meldonium and rosuvastatin significantly reduces the central and peripheral hemodynamics and vascular stiffness in patients with stage 3 CKD with hypertension. In patients with grade 1 and 2 hypertension, as well as in patients with stage 3 CKD, in combination with hypertension, who received meldonium at a dose of 1000 mg per day as part of combination therapy, a significant dynamic of quality of life indicators was observed.
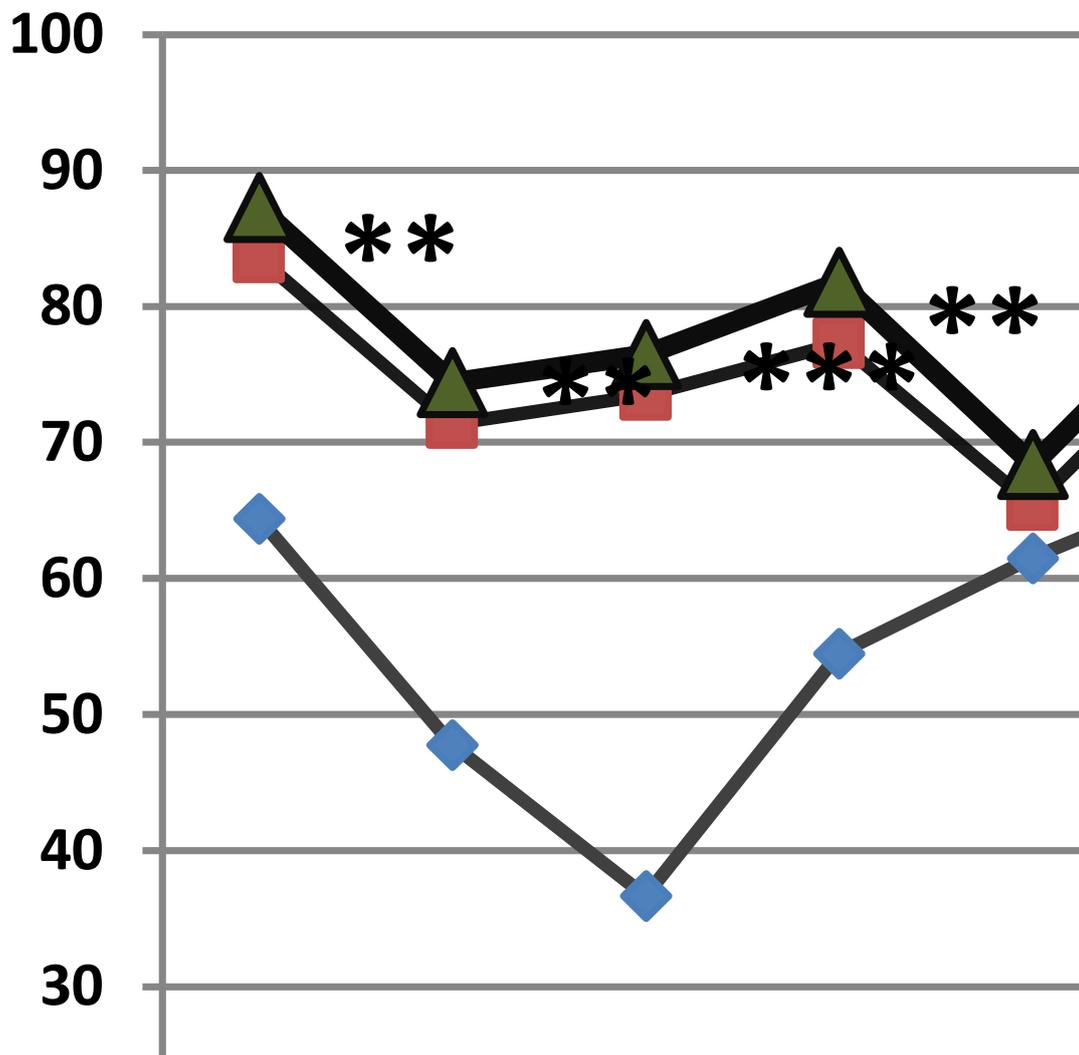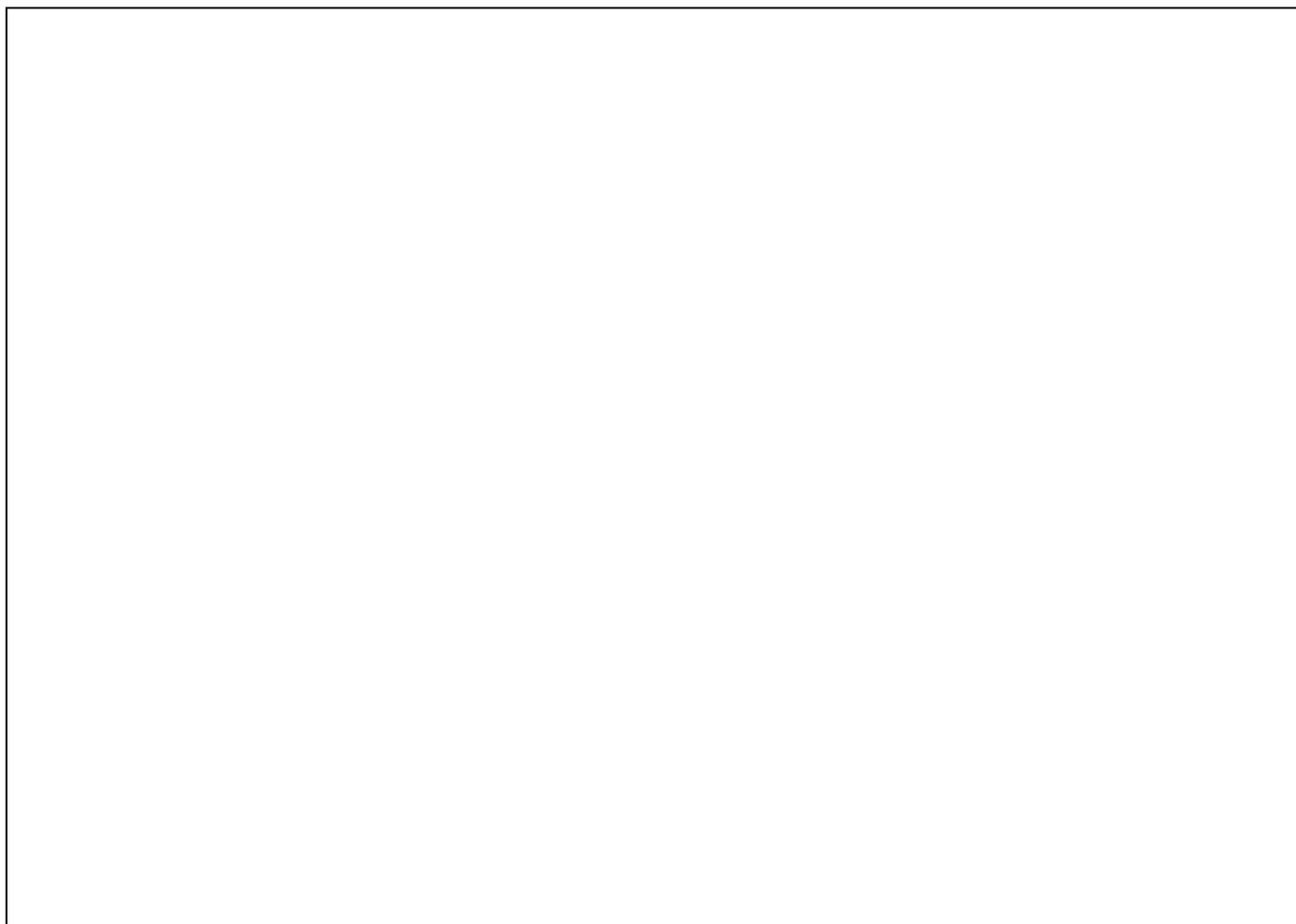
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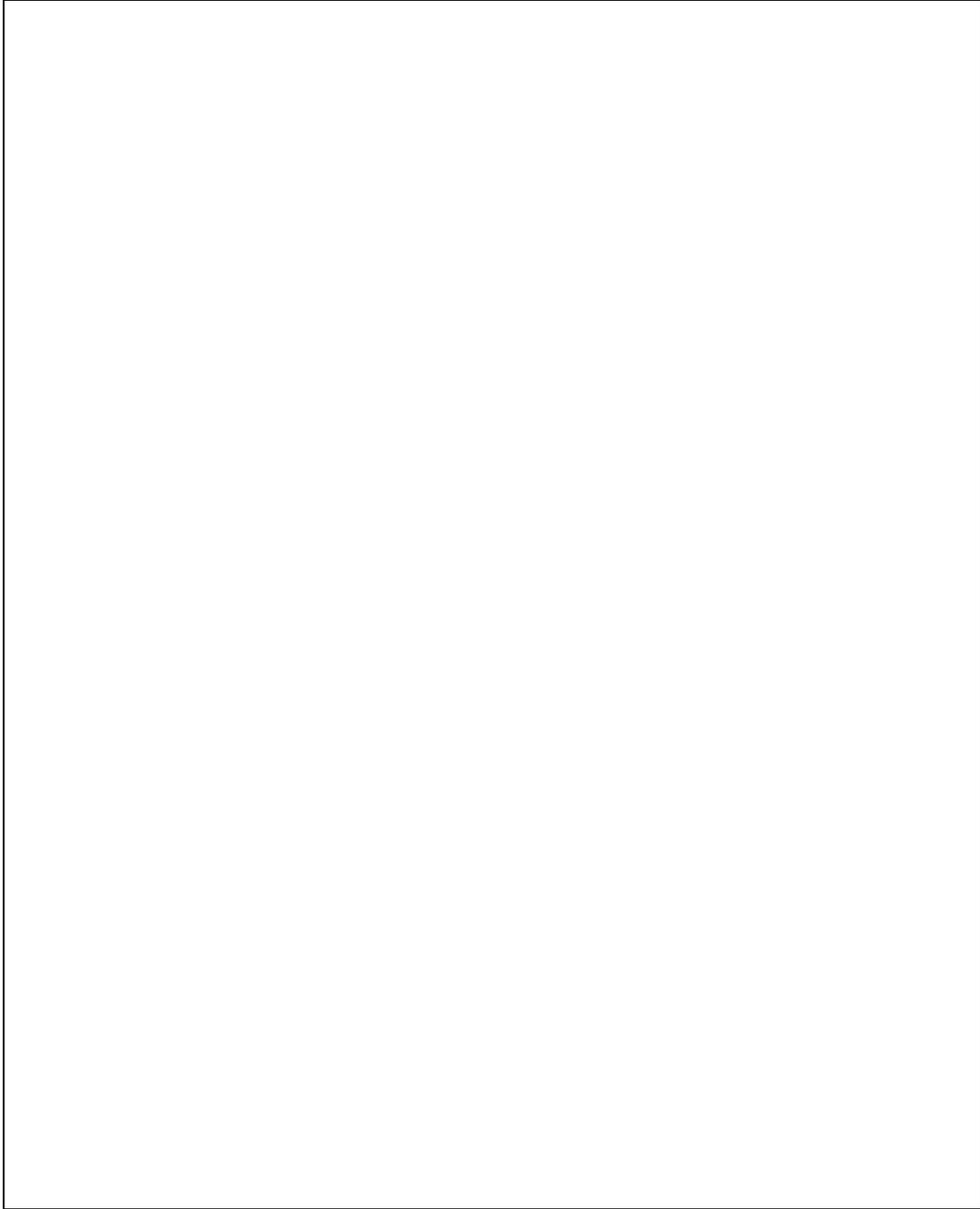
b

c

Fig. 1. Dynamics of QOL parameters of patients of the 1st (a), 2nd (b), 3rd (c) groups during treatment.

Note: ** - differences with the initial indicator are statistically significant, $p < 0.05$, ** - $p < 0.01$, *** - $p < 0.001$

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